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Management of rapid eye movement sleep behavior disorder in patients with Parkinson's disease

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MANAGEMENT OF RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER IN PATIENTS WITH PARKINSON’S DISEASE

by

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MICHAEL CAMERON JEFFRIES

ABSTRACT

Among all of the devastating effects that Parkinson’s disease (PD) has on an individual, sleep dysfunction is one that can have a profound effect on the entire family of the patient. The most potentially destructive of these sleep syndromes being that of Rapid Eye Movement Sleep Behavior Disorder (RBD). This disorder not only causes sleep impairment to the patient, but can occasionally result in life-threatening injury to the individual or their bed partner.

While this condition is manageable with medication, the current treatment of choice is a long-acting benzodiazepine, clonazepam. This drug, while effective in treating RBD, comes with a significant burden of side effects. Patients with neurodegenerative disorders, like PD, are at even higher risk of suffering the negative impacts of this treatment.

One potential alternative treatment that has been considered is a supplement of exogenous melatonin, a hormone that plays a role in maintaining one’s circadian rhythm. Several small case studies have shown potential efficacy of this treatment, and with very few side effects. However, this efficacy has not yet been proven by randomized clinical trial.

This proposed study will perform a double-blind randomized clinical trial of melatonin vs. placebo in a population of PD patients with RBD. Subjects will be analyzed
via polysomnographic sleep study, where symptoms will be scored on the RBD Severity Scale (RBDSS) at baseline and after a treatment intervention. Statistical analysis will then ascertain whether or not a significant symptom reduction is seen following melatonin treatment, compared to a group receiving placebo.

If melatonin proves to be efficacious in this patient population, this would give clinicians a new treatment option to consider to effectively manage symptoms of RBD with a much lower risk of potentially harmful side effects. Finding an effective method of managing this condition, the prevalence of which continues to rise worldwide, will have a great impact on improving the safety and quality of life of these patients.
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LIST OF ABBREVIATIONS

AAAD ................................................................. Aromatic L-amino acid decarboxylase
ANOVA ............................................................. Analysis of Variance
COMT ............................................................... Catechol O-methyltransferase
DLB ................................................................. Lewy Body Dementia
EEG ................................................................. Electroencephalogram
EKG ................................................................. Electrocardiogram
EMG ................................................................. Electromyography
FDA ................................................................. Food and Drug Administration
IRB ................................................................. Institutional Review Board
MAO-B ............................................................ Monoamine oxidase B
MSA ................................................................. Multiple System Atrophy
NMDA ............................................................. N-methyl-D-aspartate
OSA ................................................................. Obstructive Sleep Apnea
PD ................................................................. Parkinson’s disease
PSG ................................................................. Polysomnography
RBD ............................................................... Rapid Eye Movement Sleep Behavior Disorder
RBDSS ......................................................... Rapid Eye Movement Sleep Behavior Disorder Severity Scale
REM ............................................................... Rapid Eye Movement
RWSA ........................................................... REM Sleep without Atonia
SCN ............................................................... Suprachiasmatic Nucleus
INTRODUCTION

Background

Rapid Eye Movement Sleep Behavior Disorder (RBD) is clinically defined by a loss of one’s skeletal muscle atonia that normally occurs during the rapid eye movement (REM) phase of sleep. This disorder is associated with motor activity during REM sleep, as well as dream enacting behaviors. These movements can range from benign muscle twitching to aggressive, potentially violent movements which can frequently pose a risk of harm to both the individual and their bed partner. It is estimated that approximately one-third of Parkinson’s disease patients will experience RBD symptoms during or prior to the onset of the neurodegenerative symptoms of PD.¹ The disorder has a tendency to affect individuals over the age of 50, and has a male predominance.²

Statement of the Problem

Currently, the standard of care for patients suffering from this condition is treatment with clonazepam, a benzodiazepine. This treatment carries its own significant risks and side effects, including tolerance and dependence. In patients suffering from the neurodegenerative pathology of Parkinson’s disease, treatment with a benzodiazepine can lead to lingering sedative effects during daytime hours, as well as further loss of physical coordination leading to falls and injury.² In elderly patients, clonazepam also has been shown to lead to higher incidence of obstructive sleep apnea and decline in cognitive function.¹ Melatonin on the other hand seems to carry much fewer side effects, and seems to have very little risk of dependence. In small case studies, melatonin
supplements have shown to be successful in decreasing the symptoms of RBD.\textsuperscript{1,3,4} However, to this point, no randomized clinical trials have directly analyzed the efficacy of melatonin in managing symptoms of RBD, which is necessary to determine whether melatonin could be effective for pharmacologic management of RBD in Parkinson’s disease patients.\textsuperscript{5}

**Hypothesis**

The addition of a melatonin supplement at bedtime will decrease symptoms of REM Sleep Behavior Disorder in patients with Parkinson’s disease with greater efficacy than a placebo.

**Objectives and specific aims**

In conducting this research, the overall goal is that a safer, more efficacious therapy for treating RBD symptoms can be recommended. If the hypothesis of this study holds true, ideally a new first-line treatment of melatonin can be recommended for Parkinson’s patients with RBD, which will decrease the likelihood of injury to the patient and their bed partner during sleep, but also have a low side effect profile to ensure that the patient remains safe and fully functional during wakeful hours. Specific aims of this study will include:

- Determine whether treatment with melatonin will bring about a greater decrease in the symptoms of RBD compared to a placebo.
• Study the aforementioned objective in a population of patients with Parkinson’s disease, who are at increased risk for RBD, and at increased risk for negative side effects from treatment with benzodiazepines.
REVIEW OF THE LITERATURE

Overview

Parkinson's disease

The disease that is currently known as Parkinson’s disease was first described by John Parkinson in 1819. Initially named “Shaking Palsy” or “Paralysis agitans”, Parkinson described the characteristics of the disease as “Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being un-injured”.

From this initial description of the disease nearly two hundred years ago, much has changed in terms of our knowledge and understanding of the disease process, yet the fundamental clinical diagnosis is still based off the cardinal symptoms that he describes; that of tremor, bradykinesia, rigidity, and postural instability. However, it is now understood that these four cardinal symptoms are associated with a broad range of neurodegenerative disorders, and therefore this clinical presentation is more properly classified as parkinsonism syndrome. When a patient is found to possess the diagnostic criteria for parkinsonism, the differential diagnosis certainly includes Parkinson’s disease, but also Essential tremor, Vascular parkinsonism, Dementia with Lewy bodies, Progressive supranuclear palsy, Multisystem atrophy, Corticobasal degeneration, and many other secondary forms of parkinsonism. Distinguishing these conditions from one another can be very difficult for a clinician, especially in the early stages of disease; yet diagnostic accuracy is incredibly important for proper therapeutic intervention. Error
rates in diagnosing Parkinson’s disease, even by movement disorder specialists, has been shown to be as high as 24%. It has been estimated that Parkinson’s disease currently affects about 1 million individuals in the United States. The disease has an affinity toward the male gender, and increases in prevalence with advanced age, rarely affecting those under age 40. Approximately 1% of the population of individuals over age 60 are estimated to be afflicted with the disease, which is steadily increasing as the population ages. It has not been shown that there is any increased likelihood of PD among specific races or ethnic groups. The worldwide prevalence of this disease is expected to double from 2005 to 2030; although this may be a testament to the fact that individuals receiving treatment are living longer with the disease.

The pathogenesis of PD is a constantly evolving picture which has undergone decades of intense study. To this day, the etiology of this condition is thought to be multifactorial, including several potential genetic predisposing factors. Family history may play a role, where approximately 10-15% of affected individuals report a positive family history of a similar disorder. To this date, approximately 10 gene loci have been found to have an association with PD, however, no single gene mutation has been found to lead to the disease.

In the late 1950’s, it was discovered that there was a link between dopamine deficiency and the development of PD. More recent studies of the brains of PD patients using positron emission tomography have shown that there is a decrease in neuronal uptake of radiolabeled 18F-fluorodopa in the striata. This suggests that impaired
neurotransmission of dopamine may be the contributing factor to the pathogenesis of PD. It has been found that patients with PD undergo a selective loss of neurons within the substantia nigra pars compacta, which project to the striata and are responsible for the release of dopamine. This is the initial step in the signaling pathway leading to the motor cortex. It is estimated that when at least 50% of these neurons have been lost, parkinsonian features begin to arise. Additionally, in the early 1900’s Friedrich Heinrich Lewy found that when microscopically examining the neurons of PD patients, they were noted to have proteinaceous cytoplasmic inclusion bodies. Now known as Lewy bodies, these aggregations of alpha-synuclein protein are considered one of the common pathologic factors associated with PD as well as several other neurodegenerative conditions. It remains unknown whether this phenomenon is a causative factor of the disease, or simply a result of other pathologic factors.

The symptoms associated with PD can be broken down into two categories, motor and non-motor symptoms. The motor symptoms are the most characteristic of the disease, and include those previously mentioned: tremor, bradykinesia, rigidity, and postural instability. The non-motor symptoms, while not as specific to PD, can be equally detrimental to patient’s quality of life, and occasionally can even be life threatening. These symptoms broadly include neuropsychiatric symptoms, sleep disorders, autonomic dysfunction, gastrointestinal symptoms, sensory symptoms, and many others.

Of the motor symptoms of PD, the most pathognomonic association of the disease is that of a resting tremor. The resting tremor of PD is typically noted to develop asymmetrically in a single limb, most often a hand. Tremulousness of the affected limb
only occurs when voluntary motion is not taking place; once the individual initiates movement of the limb the tremor will cease. This differentiates the tremor of PD from that of Essential tremor, in which tremulousness will be brought on when the individual is performing voluntary movement of the affected limb. Classically, walking tends to bring about the resting tremor of PD. The tremor can also affect the chin, jaw, and tongue, but rarely causes a tremor of the entire head. Tremor can also be absent in approximately 20% of individuals with PD.9

Similar to the resting tremor, bradykinesia associated with PD also tends to occur asymmetrically. This symptom is most typically reported by patients as a unilateral weakness of a either a hand or leg, however, no strength deficits are usually noted on physical exam. However, when assessing a PD patient’s repetitive movement ability via finger tapping or toe tapping, the examiner may notice that the patient’s movement will decrease in speed, amplitude of motion may be reduced, and cadence of rhythm may become irregular over time while performing this exercise. This can manifest for the patient at home as a difficulty with repetitive motions such as brushing ones teeth. The patient may also report difficulties at home with activities that require fine motor coordination, such as buttoning a shirt, or writing.9 There also tends to be slowness in both initiating and carrying out movements, and loss of some spontaneous movement altogether.14

The rigidity of PD is often described by the patient as “stiffness associated with vague aching and discomfort of a limb”.9 These vague symptoms often lead to misdiagnosis as a simple musculoskeletal injury. This rigidity can eventually lead to
complete immobilization of a joint, such as frozen shoulder, but this is more typical in advanced disease.\textsuperscript{9}

Postural instability is another frequent manifestation of PD, which tends to arise with more advanced disease. Most commonly noted is a “simian posture” or an increased kyphosis of the thoracic spine. There can also be lateral bending of the trunk, flexion of the forearms, ulnar deviation of the digits, and inversion with plantar flexion of the feet.\textsuperscript{14}

The combination of these cardinal symptoms of PD tend to lead to other characteristic findings in these patients. Gait disturbance is common, with the classic finding of the “shuffling gait” with dragging of one or both feet and decreased arm swing, as well as a narrow separation of the feet. Transitioning from sitting to standing position tends to be difficult for these patients. Handwriting alteration is another common characteristic of PD patients, where one’s handwriting tends to become noticeably smaller with irregularities in letter sizing and spacing.\textsuperscript{9} Speech can become altered as well, with monotony and low volume commonly observed, and occasionally notable dysarthria.\textsuperscript{14}

While the motor symptoms of PD are the most characteristic of the disease, the non-motor symptoms tend to be equally detrimental to the quality of life of these patients. The non-motor symptoms originate from a similar pathophysiologic mechanism as the motor symptoms, resulting from the deterioration of dopaminergic neurons within certain key areas of the brain. Often the non-motor symptoms will precede the motor symptoms, and currently research is being pursued to utilize these early onset symptoms to make an earlier diagnosis of PD. Braak and colleagues have designed a staging system that
correlates the non-motor and motor symptoms of PD to a patient’s likely stage of disease based upon their level of neurodegeneration. Braak stage 1 is associated with degeneration of the olfactory bulb and will lead to olfactory dysfunction in the patient. Braak stage 2 is associated with early changes to the lower brainstem and is characterized by sleep dysfunction, including REM sleep behavior disorder, and autonomic instability. Braak stage 3 and 4 signify the beginnings of the motor symptoms of PD where the classic tremor, bradykinesia, and rigidity begin to appear, and also when PD is formally diagnosed. These stages are associated with the loss of neurons within the substantia nigra. Braak stages 5 and 6 are associated with the development of Lewy bodies and the development of cognitive deficits, psychiatric symptoms, and visual hallucinations. Many of the non-motor symptoms, however, do not neatly fit into one of the aforementioned Braak stages, and can seemingly affect patients at any stage of the disease.\(^{13}\)

One of the earliest, more prominent symptoms that occurs in PD is that of sleep dysfunction. Nearly all patients with PD have been shown to have some form of sleep dysfunction. While the cause of this dysfunction is multifactorial, it is thought that degeneration of the brainstem and thalamocortical pathways involved in sleep regulation are responsible for these symptoms. Sleep disturbances can vary from insomnia, to disruption of normal circadian rhythm cycles, to loss of normal muscle atonia during REM sleep, known as REM sleep behavior disorder. Alterations in normal sleep architecture can lead to issues such as decreased sleep latency similar to narcolepsy, disordered breathing or sleep apnea, nocturia, and poor quality sleep overall. Up to 50%
of PD patients report excessive daytime sleepiness and falling asleep throughout the day.  

Neuropsychiatric disorders are another common non-motor symptom of PD. Most typical among these are mood disorders. Depression is one of the most typical to be seen in early stages of PD, the cause of which seems to be a combination of pathological PD changes and simply reaction to diagnosis of a neurodegenerative disease. However studies have also shown that a history of depression may be a risk factor for PD in itself, where one study showed that patients with a clinical history of depression were 13.3 times more likely to develop PD than a control group. Anxiety and apathy are also common psychiatric symptoms facing PD patients, however, this is more commonly a side effect of anti-parkinsonian drug therapy rather than part of the disease course. Frank psychosis and visual hallucinations can occur with PD as well, but this is more typically seen in advanced stage disease due to the development of Lewy bodies in the temporal/limbic cortex. However, psychosis can also be a result of antiparkinsonian therapy with dopamine agonists, levodopa, amantadine, and anticholinergics.

Cognitive impairment is associated more typically with end-stage disease, and has an incidence in PD that is four times greater than the general population. The pathophysiology leading to dementia and cognitive deficits is typically the propagation of Lewy bodies within the cortex of the brain, which occurs in advanced disease. Age is the primary risk factor for development of dementia in PD, but also included are male gender, poor socioeconomic status, and increase severity of motor symptoms. The most common cognitive deficits noted in PD patients are attention, executive function, and
visuospatial awareness. Decreased cognitive function is associated with a worse quality of life, worsened prognosis, and greater likelihood that the patient will require placement in a long term care facility.\textsuperscript{15}

Autonomic dysfunction is a manifestation that can occur frequently in PD, although the pathophysiology is quite complex and not fully understood. Underlying these symptoms is the neurodegeneration of various nuclei responsible for control of sympathetic preganglionic neurons in the descending pathways; as well as impaired function of cholinergic, monoaminergic, and serotonergic nuclei. Most common symptoms reported in PD patients include orthostatic hypotension, constipation, bladder dysfunction, erectile dysfunction, and hyperhidrosis. Autonomic dysfunction is typically a manifestation of more advanced stage PD.\textsuperscript{13}

Many tools have been developed and utilized to determine the stage and severity of disease in PD, however, the scale developed by Hoehn and Yahr in 1967 remains one of the most widely used clinical measures to report the patient’s degree of disability.\textsuperscript{14} In 2004, the Movement Disorder Society Task Force adapted a Modified Hoehn and Yahr Scale with additional increments, allowing for more specific staging of Parkinson’s disease progression and disability, which is now more commonly utilized.\textsuperscript{16}
Table 1. Modified Hoehn and Yahr Scale. (Used to rate the progression of disease and degree of disability of PD patients)

<table>
<thead>
<tr>
<th>“Stage 1.0”</th>
<th>Unilateral involvement only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1.5</td>
<td>Unilateral and axial involvement</td>
</tr>
<tr>
<td>Stage 2.0</td>
<td>Bilateral involvement without impairment of balance</td>
</tr>
<tr>
<td>Stage 2.5</td>
<td>Mild bilateral disease with recovery on pull test</td>
</tr>
<tr>
<td>Stage 3.0</td>
<td>Mild to moderate bilateral disease; some postural instability; physically independent</td>
</tr>
<tr>
<td>Stage 4.0</td>
<td>Severe disability; still able to walk or stand unassisted</td>
</tr>
<tr>
<td>Stage 5.0</td>
<td>Wheelchair bound or bedridden unless aided</td>
</tr>
</tbody>
</table>

As the pathology of PD directly relates to the loss of dopamine neurotransmission to the striatum, it was proposed nearly 50 years ago that intake of an exogenous dopamine supplement or dopaminergic agonist could potentially reverse the effects of the disease. Dopamine itself was found to be unable to cross the blood brain barrier, making it an ineffective drug. Thus levodopa, an amino acid compound which acts as an intermediate in the dopamine synthesis pathway, was found to successfully cross the blood brain barrier and then undergo conversion to dopamine. The ELLDOPA (Earlier versus Later Levodopa Therapy in Parkinson’s disease) study found Levodopa to have a dose-dependent improvement in parkinsonian symptoms over a 40 week treatment period compared to placebo. This study also showed Levodopa to have many neuroprotective benefits, showing a lesser degree of disease progression and neurodegeneration compared to those receiving placebo.

Levodopa therapy does not come without side effects however, where nearly one half of patients within five years of initiating treatment were shown to have a classic side
effect profile of motor fluctuations and dyskinesia. Younger patients seem especially susceptible to these effects. It has been found however, that Levodopa treatment with the addition of a dopamine agonist may decrease the risk of such side effects. Also postponing the initiation of Levodopa treatment or utilizing a different treatment option during mild to moderate stages of disease may prove beneficial in lowering risk of motor side effects.¹¹

Levodopa therapy can lead to peripheral dopaminergic side effects as well, including hypotension and nausea. To avoid these effects, the drug is now typically prescribed in combination with a peripheral acting aromatic L-amino acid decarboxylase (AAAD) inhibitor, also known as carbidopa. In addition, Levodopa/carbidopa (Sinemet) is often prescribed with a catechol O-methyltransferase (COMT) inhibitor, also called entacapone. This prevents O-methylation of Levodopa and prolongs its effects.⁹

Other second line treatment options for the motor symptoms of PD include anticholinergics, selective MAO-B inhibitors, and NMDA antagonists (amantadine). Anticholinergics are very rarely used due to their poor side effects, but can be helpful in patients in whom tremor remains a life-altering symptom and is not controlled by other medications. MAO-B inhibitors and amantadine have few side effects and have relatively simple dosage titration, however, these drugs alone are not particularly efficacious at treating motor symptoms of PD. Some research suggests however that MAO-B inhibitors, among other drugs, may have some neuroprotective benefits and may slow progression of disease.⁹
For severe motor symptoms that remain refractory to medications, surgical intervention can be highly efficacious. The typical surgical approach is known as deep brain stimulation with implantable electrodes placed into the thalamus via thalamotomy. Pallidal stimulation and sub-thalamic stimulation are occasionally utilized as well. The FDA has approved deep-brain stimulation for patients “as an adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson’s disease that are not adequately controlled by medication.” This intervention is only performed in patients who have failed several attempts at controlling symptoms with various medication combinations, patients who are severely impaired in gait, balance, and speech, and patients in whom dyskinesias and other medication related side effects are an issue. Deep brain stimulation works by altering the pattern of neuron activity in the basal ganglia, increasing local neurotransmitter release, and increasing blood flow to promote neurogenesis. However, it remains largely unknown as to how this treatment specifically alters the symptoms of PD.

**REM Sleep Behavior Disorder**

REM Sleep Behavior Disorder (RBD) is a parasomnia which was first described by Schenck et al in 1986. The condition is described as a loss of the normal muscle atonia that occurs during the REM phase of sleep. Patients with this disorder tend to exhibit motor activity during sleep, typically in association with dreaming. This activity can be as subtle as a minor twitch, or be violent and aggressive, potentially causing harm to themselves or their bed partner. More severe behaviors associated with RBD can be
quite complex, including hitting, grabbing, trying to defend oneself, leaping out of bed, and occasionally walking. Some patients vocalize during sleep, either as incoherent mumbling or sometimes as fluent speech. Typically these behaviors are associated with vivid, typically unpleasant dreaming. In one study of 58 patients, it was found that 91% of patients who showed motor behaviors during sleep were found to have had dreams where they were in danger, either fighting or fleeing.\textsuperscript{20}

RBD has been found to have a male predominance, and tends to affect those in the age range from 40-70.\textsuperscript{21} A great deal of research has been compiled showing an association of RBD development in patients with neurodegenerative disorders, especially alpha-synucleinopathies. RBD has been shown to affect nearly 60% of patients with PD, and 80-100% of patients with Lewy body dementia (DLB) and multiple system atrophy (MSA).\textsuperscript{20} Interestingly, the onset of RBD tends to precede the more notable symptoms of these neurodegenerative disorders by years or even decades, so researchers are currently looking for a way to predict the onset of such disorders based on the onset of RBD symptoms.\textsuperscript{21}

To make a clinical diagnosis of RBD, a clinician must note the following criteria in the patient, from the 2005 edition of the International Classification of Sleep Disorders:

i. “Presence of REM sleep without atonia (RWSA) on polysomnography (PSG)

ii. At least one of the following:
a. Sleep-related, injurious, potentially injurious or disruptive 
behaviours by history (i.e. dream enactment behaviour) and/or 
b. Abnormal REM sleep behavior documented during 
polysomnographic monitoring.

iii. Absence of EEG epileptiform activity during REM sleep unless 
RBD can be clearly distinguished from any concurrent REM sleep-
related seizure disorder.

iv. The sleep disorder is not better explained by another sleep 
disorder, medical or neurological disorder, mental disorder, 
medication use of substance use disorder.”

The pathophysiology behind RBD is quite complex, and a great deal remains to 
be uncovered. In patients with RBD, spinal interneurons are stimulated during REM sleep 
and have an excitatory effect on muscle fibers. These spinal interneurons receive 
excitatory stimulation from locomotor generators, and inhibitory stimulation by a 
complex network of nuclei, whose net effect in non-RBD individuals is overall inhibition 
of spinal interneurons leading muscle atonia during REM sleep. In patients with RBD, 
there is a defect of the sublaterodorsal nucleus in its ability to stimulate the inhibitory 
effects onto the spinal interneurons, thus allowing excitation of skeletal muscle fibers.

As RBD symptoms can be incredibly dangerous and at times life-threatening, it is 
incredibly important that this condition be effectively addressed and treated. Currently, 
the first-line drug therapy for RBD is clonazepam, a benzodiazepine. This medication
however, comes with somewhat dangerous risks and side effects, including tolerance and
dependence, daytime sleepiness, impairments in cognition, and worsening physical
coordination. It can cause progression of pre-existing sleep disorders as well, such as
obstructive sleep apnea. In elderly patients, and especially patients with
neurodegenerative disorders, these side effects can be incredibly harmful, and impair
their already deteriorating quality of life.\textsuperscript{24}

Some studies have looked at the use of a melatonin supplement to be used as
treatment for RBD. Melatonin has a much lower side effect profile, and seems to be just
as efficacious as clonazepam in decreasing the symptoms of RBD. Additionally,
melatonin can be beneficial in correcting the circadian rhythm of these patients, whose
sleep cycles tend to have some degree of impairment.\textsuperscript{25}

\textbf{Existing research}

For a clinician to choose a medication to properly manage the symptoms of RBD
in patients, they must take into consideration both the efficacy of the treatment, and the
side effect profile of the drug. Especially in patients with PD, who are typically advanced
in age, and have neurodegenerative disease, finding a treatment that will not cause the
patient additional harm is extremely important. The standard of care currently is that of
clonazepam. This was initially determined to be the gold standard treatment by Schenck
et al, who initially discovered this disease.\textsuperscript{19} While clonazepam has been shown to be
effective in many patients for symptom management, the side effects that this drug poses
to patients are quite significant.
Clonazepam is a long-acting benzodiazepine with sedative properties, and has a half-life of between 20 and 50 hours. Its mechanism of action in treating RBD is not fully understood, but it has been shown that the drug successfully “reduces phasic EMG activity but does not restore tonic REM sleep muscle inactivity”. In a retrospective analysis performed by Anderson et al, 54% of patients prescribed clonazepam for treatment of their RBD symptoms reported an overall benefit from the medication. Within this same group however, 58% reported moderate or severe side effects as a result of the drug. Most of these patients requested to either stop the medication, switch to an alternative treatment, or decrease the dose, despite seeing relief in their sleep symptoms. The most common reported side effects from this study were lingering daytime sleepiness, confusion, and cognitive impairment. These authors concluded that, while clonazepam seems to be an effective treatment for RBD, the side effects that result from its use lead it to be an unsatisfactory therapy for this condition.

While several other drugs are being researched as potential treatments for this disorder, one that seems to show promising results in terms of efficacy and low risk of side effects is exogenous melatonin. Melatonin is a hormone that seems to play a role in the maintenance of circadian rhythm in humans. Secretion of melatonin has been shown to be highest in the late evening, and lowest in the morning; and seems to be inversely related to times of peak sunlight exposure. The area of the brain with greatest receptor density for melatonin is the suprachiasmatic nucleus (SCN), which seems to be the region that drives circadian rhythm synchronization in mammals. Exogenous melatonin supplementation has shown several benefits in humans to date, including recovery from
jet lag, facilitating earlier phase sleep in patients with sleep phase-delay syndromes or shift work disorders, and restoring a proper day-night sleep cycle in blind individuals. The overall effect of exogenous melatonin seems to be that of restoring or shifting one's circadian rhythm. Recent data from SCN lesion studies have shown that circadian rhythms and REM sleep continuity are impaired by lesions to the SCN; which could play a role in the pathophysiology of RBD. Kunz and Bes hypothesized that among other things, one of the primary driving factors in the development of RBD is circadian rhythm desynchronization, which exogenous melatonin could help to restore.²⁶

To date, several studies have been performed that have shown a significant improvement in RBD symptoms with melatonin treatment. The first study to examine this therapy was performed by Kunz and Bes in 1999 in a study of six patients with RBD who were given open-label melatonin treatment, and followed with polysomnographic studies, actigraphy, and sleep diaries. The study results showed significant clinical improvement in patient’s RBD symptoms, with polysomnographic improvement in REM sleep parameters and a decrease in motor activity during sleep with melatonin supplement.²⁶

In 2001, Takeuchi et al. reconfirmed these findings in a study of 15 patients which analyzed similar parameters, and additionally analyzing patient’s baseline melatonin secretion. This study again showed a significant suppression of RBD associated sleep behaviors, especially in patients with low baseline melatonin secretion.⁴

In 2003, a study by Boeve et al. similarly assessed the outcomes of RBD symptoms with melatonin therapy, but specifically looked at patients with concurrent
neurodegenerative disorders. The decision to study this population of patients was decided based on the fact that these are the patients who tend to be at increased risk of developing RBD, but also because these patients are at greater risk of negative side effects from treatment with clonazepam. This study showed a persistent benefit with melatonin in 57% of patients with very few reported side effects.\(^3\)

While melatonin seemed to show very positive results in treating RBD symptoms in these preliminary studies, it remained to be shown how this therapy compared to the first-line treatment, clonazepam. In 2013, McCarter et al. performed a retrospective analysis of RBD patients treated at Mayo Clinic from 2008-2010 comparing those treated with clonazepam to those treated with melatonin. The findings of this study showed that melatonin and clonazepam showed similar results in terms of treatment efficacy, however, the side effects associated with clonazepam were far greater than those treated with melatonin. Interestingly however, in a subgroup analysis of patients with neurodegenerative disorders, melatonin-treated patients showed a statistically significant reduction in RBD symptom ratings, while clonazepam-treated patients showed a reduction that was not statistically significant. This study also determined a median effective dose of both melatonin and clonazepam, 6mg and 0.5mg respectively.\(^25\)

While many studies simply analyze RBD symptoms based on subjective data from patient and family member reports of symptoms, a more objective measurement of RBD symptoms would provide for a more accurate study of treatment efficacy. In 2011, Sixel-Döring et al. devised an effective scale to quantify severity of symptoms in RBD patients. This RBD severity scale (RBDSS) is based on polysomnographic analysis of
patients, and specifically rates patients based on motor symptoms and nighttime vocalizations. Motor symptoms are based on a 0-3 scale, where 0 = no movement, 1 = slight movements or jerks, 2 = movements involving the proximal extremities, and 3 = axial movement or bed falls. Vocalizations are scored either 0 or 1, based on their absence or presence respectively. This scale was slightly modified when it was utilized in a study by Ferri et al., to include half-point intervals (0 – 3.5), allowing for better statistical analysis of the data.

Overall, several studies have shown to some degree that treatment with exogenous melatonin can bring about a reduction in the potentially dangerous symptoms associated with RBD. Melatonin also seems to be associated with a very low risk of side effects. While evidence thus far has shown clonazepam to be equally efficacious in reducing RBD symptoms, this therapy comes with a much higher side effect burden. These side effects tend to be even more pronounced in patients who have neurological disorders such as Parkinson’s disease. To this date, however, no randomized placebo-controlled trials have directly compared melatonin to a placebo in terms of efficacy in decreasing RBD symptoms. Furthermore, no studies have analyzed this treatment use specifically in a population of Parkinson’s patients.
METHODS

Study design
The proposed study will be a double-blind, placebo-controlled randomized clinical trial comparing two treatment arms, melatonin and a placebo.

Study population and sampling
The population to be studied in this trial are patients with diagnosed Parkinson’s disease, specifically early-moderate disease (stage III or lower on Modified Hoehn and Yahr scale\textsuperscript{16}). Selection criteria will also include a formal diagnosis of RBD based on International Classification of Sleep Disorders diagnostic criteria.\textsuperscript{22} Patients will be excluded if they have any poorly controlled comorbid medical conditions that affect sleep (such as OSA requiring nighttime ventilation assistance), or are prescribed any medications that have an effect on sleep, such as benzodiazepines, anti-psychotics, and antidepressants. Patient’s may remain on a standard PD medication regimen and will be instructed that this regimen may not be changed while they remain involved in the study. No exclusions will be made based on patient demographics (age, gender, ethnicity, etc.) An appropriate sample size of at least 52 patients will be selected in order to achieve an alpha value of 0.05, a beta value of 0.2, and to bring about an estimated mean clinical decrease of at least 0.5 on the REM Behavior Disorder Severity Scale (RBDSS). These parameters were determined using a baseline mean RBDSS score of 2.1, based on analysis of the tool by Sixel-Döring et al.\textsuperscript{27}, and an estimated mean RBDSS score of 1.6
following treatment. Sample size was determined using an online sample size calculator.²⁹

**Treatment (or intervention)**

The intervention performed in this study will be initiation of a treatment of melatonin or a placebo. Subjects assigned to the melatonin treatment arm will be given Melatonin Quick-Sorb (Great Earth, Los Angeles, CA, U.S.A), as was used in the initial melatonin study by Kunz and Bes.²⁶ The dose of melatonin administered will be 6mg, as this was the median effective dose determined by McCarter et al.²⁵ Subjects will be randomly and blindly assigned to a medication, and instructed to take the assigned medication for a period of six weeks. During the treatment month, subjects will be instructed to take the assigned medication each night, approximately 30-60 minutes before they plan to sleep. Subjects will also be asked to maintain a fairly consistent bedtime during their time in the study, to promote circadian rhythm regulation.

**Study variables and measures**

The independent variable of this study is the initiation of a medication intervention with either melatonin or a placebo. The dependent variable to be analyzed will be the subject’s score on the REM Behavior Disorder Severity Scale (RBDSS) during polysomnographic study. The study will utilize the modified RBDSS scale as was used by Ferri et al. which will evaluate subjects on a 0 – 3.5 scale.²⁸ Comparison will be made between the patient’s baseline RBDSS score and their score following six weeks of treatment. The primary end point of the study is to determine if there is a significant change in the
patients RBDSS score following a medication intervention, compared to the subject’s baseline.

**Recruitment**

Subjects will be referred to the study by movement disorder specialists at Boston Medical Center. Patients who will be referred will have an existing diagnosis of Parkinson’s disease, who also report sleep dysfunction, not currently being controlled with medications. Subjects will then be seen by a clinician involved in the study to ensure they meet clinical criteria for the trial.

**Data collection**

Subjects who agree to take part in the study will be asked to take part in an initial PSG study in order to formally diagnose RBD, and also to obtain a baseline analysis of their RBD symptom severity on the RBDSS. Following the initial PSG, subjects who meet criteria for the study will begin their assigned medication protocol for a six week period, and will then report for a follow-up PSG. PSG will take place in a standard sleep lab, and will follow a protocol used by Kunz and Bes in their study of RBD patients. Subjects will be in a noise-controlled environment with lights out from approximately 22:00 to 06:00. Subjects will be analyzed with EEG for sleep staging, EMG (submentalis, and left and right tibialis), EKG, and oral and nasal air flow thermistor to measure sleep respiratory patterns. The entire study will take place under video surveillance to be analyzed by a trained technician, who will score the subjects according to the RBDSS.
**Data analysis**

After baseline and post-treatment RBDSS scores are determined for each subject, the difference will be computed in order to determine the change in each patient’s symptom severity following the assigned treatment regimen. Data will be grouped according to subject’s age, and PD severity (Hoehn and Yahr scale), as these variables can have an impact on patient’s REM sleep quality. Mean and standard deviation will be calculated for both treatment groups. The melatonin and placebo group data will be compared to one another by Student’s T test. Variation amongst subjects within each group will be analyzed via ANOVA.

**Timeline and resources**

Allowing for time to plan, allocate resources, recruit patients, and receive proper approval from the IRB, the study could reasonably begin in January 2017. All subjects will require two PSG studies with a six week interim between studies. As PSG resources will most likely be limited, not all patients will be able to start and end the study at the same time. Therefore, a completion date around April 2017 would be appropriate to anticipate.

In terms of human resources that will be necessary, there will be one primary investigator in charge of project oversight. Two to three clinicians will be required for clinical evaluation of potential subjects to ensure they meet criteria for the study. One or two PSG technicians will be needed to oversee the PSG studies, as well as two individuals trained to evaluate PSGs, specifically trained in RBDSS protocol. One statistician will likely be useful as well, to assist with data analysis.
For materials, all that will be necessary are the PSG labs containing all necessary equipment for conducting the sleep studies.

**Institutional Review Board**

In order to perform research on human subjects, an application for full-board approval of the Institutional Review Board of Boston University Medical Center will be submitted. Approval from the IRB will be obtained prior to the start of patient recruitment.
CONCLUSION

Discussion

While the proposed study is unique in many ways, and will provide helpful insight that may guide future management of RBD in Parkinson’s patients, there are several weaknesses to the study design that must be considered. For one, limitations exist in the use of PSG sleep analysis. Patients will likely not sleep as well during a sleep study as they would in the comfort of their own homes, especially with the added discomfort of all the measurement tools attached to them as they sleep. Even at baseline, RBD patients will likely have great variation in their behaviors during a sleep study, so this method of analysis may prove to be a difficult tool for this study. An additional limitation to this trial is the RBDSS scale. Even using the modified RBDSS, the scale is quite limited, only allowing a rating from 0 – 3.5, hardly accounting for the vast array of behaviors that patients could present.

As far as generalizability of the study, the goal is that the population recruited will make the results highly generalizable to all PD patients with RBD. Patients at Boston Medical Center represent a highly diverse patient population, which works in favor of generalizing the data. Regardless of what insight the data provides, however, clinicians must understand that sleep is a very complex physiologic process, and it is impossible to predict how any individual patient will react to a medical intervention, especially when a comorbid neurodegenerative process is at play.

Despite the aforementioned shortcomings of this study, there are several strengths that set this trial apart from any that have been previously performed. For one, this trial
plans to provide randomized clinical trial evidence of a benefit of using melatonin in a subset of patients with RBD. No previous studies in RBD patients thus far have examined melatonin vs. placebo in a randomized clinical trial format. Furthermore, this trial is using objective data from a PSG sleep analysis. Most studies of RBD management thus far have used subjective data, such as a survey sent to patients, which comes with a significant level of recall bias and other potential distortion to the data. One of the greatest benefits this study will provide, however, is data specifically geared toward RBD patients with concurrent Parkinson’s disease. No studies to date have specifically looked at RBD treatments in this specific subset of patients.

Summary

RBD is a potentially dangerous and frightening disorder that affects over 60% of individuals with PD. Currently, the standard of care for managing these symptoms is with clonazepam. This medication can cause several detrimental side effects, especially in the PD patient population, including daytime somnolence, worsening cognitive function, and impaired physical coordination. Overall, several small case studies have shown a potential benefit from the use of melatonin for management of the symptoms of RBD. The efficacy of melatonin in managing RBD symptoms seems to be at least comparable, if not greater, than that of the current standard of care, clonazepam. However, this has not yet been shown in a randomized clinical trial.

If the hypothesis proves correct, then the proposed study will provide evidence that melatonin is an efficacious treatment option for RBD in PD patients. Further studies will need to be pursued in the future, however, to determine how melatonin directly
compares to clonazepam in its efficacy and side effect burden in treating RBD.

Additional studies will also have to be performed to determine the efficacy of melatonin for managing RBD in patients without PD, as this study is specifically focused on only the PD patient population.

**Clinical and/or public health significance**

As the population in our country becomes more advanced in age, diseases such as PD are going to continue to increase in prevalence. Modern medical advances have allowed PD patients to live longer than ever before, but with longer lifespan comes other risks that need to be properly managed. With as many as two-thirds of PD patients facing sleep dysfunction and RBD symptoms, finding an effective way of managing these patients is a significant clinical problem that needs to be addressed.

A diagnosis of PD not only puts patients at increased risk of RBD, but also puts them at greater risk for being negatively impacted by treatment with clonazepam. By studying a population of PD patients for this study, ideally melatonin as a treatment alternative to clonazepam will prove efficacious for these individuals. This will drastically improve quality of life in these patients, allowing them to have more energy during wakeful hours, less cognitive impairment, and no further deterioration of their physical coordination. This simple medication change could help PD patients to be safer in their homes, potentially allowing them to continue living independently for a longer duration of time. Ideally, melatonin treatment will prove to be efficacious in this population to allow for an additional treatment option available for clinicians to consider.
# LIST OF JOURNAL ABBREVIATIONS

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<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>Ann N Y Acad Sci</td>
<td>Annals of the New York Academy of Sciences</td>
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<tr>
<td>Arch Neurol</td>
<td>Archives of Neurology</td>
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<tr>
<td>Arq Neuropsiquiatr</td>
<td>Arquivos de Neuro-Psiquiatria (Portuguese)</td>
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<td>JAMA</td>
<td>The Journal of the American Medical Association</td>
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<td>J Clin Sleep Med</td>
<td>Journal of Clinical Sleep Medicine</td>
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<td>J Neuropsychiatry Clin Neurosci</td>
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REFERENCES


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EDUCATION

2014-2016  Boston University School of Medicine, Boston, MA
Master of Science, Physician Assistant Program
Degree Conferred August 2016 (expected)
Thesis: Management of Rapid Eye Movement Sleep Behavior Disorder in Patients with Parkinson’s disease

2008-2012  Truman State University, Kirksville, MO
Bachelor of Science
Major: Chemistry
Minor: Biology

EXPERIENCE

2012-2014  Phlebotomist/Lab Assistant
North Kansas City Hospital
Kansas City, MO
Responsible for collecting blood and other laboratory specimens from hospitalized patients. Also assisted with specimen processing and other clerical duties.

CERTIFICATION AND LICENSURE

2015-present  ACLS Certification

PROFESSIONAL ORGANIZATIONS

2014-present  American Academy of Physician Assistants
2014-present  Massachusetts Academy of Physician Assistants
LEADERSHIP EXPERIENCE

2014-present  
*Vice President – Carl Toney Student Society*  
Served as elected officer in PA Program Student Society

COMMUNITY SERVICE/VOLUNTEER WORK

October 2014  
*Boston Healthcare for the Homeless – Women’s Health Fair*  
Assisted clinicians in performing oral health examinations, and provided oral health counseling

October 2014  
*PA Week Coordinator*  
Organized student committee to plan outreach activities on medical school campus in honor of PA Week

2015-present  
*First year PA Student Mentor*  
Volunteered as mentor for two incoming first year PA students