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REM sleep behavior as a preclinical risk factor for Synucleinopathies

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**REM SLEEP BEHAVIOR DISORDER AS A PRECLINICAL RISK FACTOR
FOR SYNUCLEINOPATHIES**

by

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B.S., State University of New York at Binghamton, 2011

Submitted in partial fulfillment of the
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APRIL JESSICA PINTO

Boston University School of Medicine, 2013

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ABSTRACT

Objective: To determine the prevalence of REM behavior disorder in the synucleinopathy patient population, treatments used, and effectiveness of these treatments.

Background: Rapid eye movement (REM) sleep behavior disorder (RBD) is a sleep disorder characterized by loss of muscle atonia during the REM sleep stage, often manifesting in shouting, flailing, and kicking behaviors. These behaviors are generally associated with the content of the dream and patients report these dreams as unusually vivid. We have evaluated patients with Synucleinopathies (Multiple Systems Atrophy, Parkinson's disease, and Dementia with Lewy Bodies) to examine the prevalence of RBD in this population and the presence of screening practices. In addition to the typical motor symptoms of these diseases, RBD, as a non-motor symptom, is a common precursor to these disorders.

Methods: This study was conducted via a retrospective chart review and analysis

of 278 patients in the movement disorders clinic at Boston Medical Center from 2011.

Results: These patients had an average age of 71.6 years (± 8.4 years). Of these patients, 36.8% of those with Parkinson's Disease, 66.6% of those with Multiple system atrophy, 61% of those with Lewy Body Dementia and 17.9% of those with Parkinsonism were comorbid for RBD. Of all charts reviewed 73.7% of the patients were screened for RBD and 46.8% of those with this disorder were undergoing treatment for it, 37.8% were taking melatonin(average 3.5mg ± 1.1 mg) with a 57.1% improvement, while 62% were on Clonazepam(average .5mg $\pm .16$ mg) with a 56.5% improvement. 32.9% of our RBD population was found to be on SSRIs. 72.2% of our RBD population was male.

Conclusion: It is evident that RBD has a high prevalence in this population and may be able to serve as a pre-clinical risk factor and diagnostic measure. Further study of the correlation between RBD and Synucleinopathies may allow for earlier and more accurate diagnosis, thereby having implications in the treatment of these neurodegenerative disorders.

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ABBREVIATIONS

AASM	American Academy of Sleep Medicine
DLB	Lewy body dementia
EEG	Electroencephalogram
EMG	Electromyogram
GABA	Gamma-aminobutyric acid
HY	Hoehn and Yahr
ICSD-2	International classification of sleep disorders-2
iRBD	Idiopathic REM sleep behavior disorder
LB	Lewy body
LDTN	Laterodorsal tegmental nucleus
LN	Lewy neurite
LPT	Lateral pontine tegmentum
MCRF	Magnocellular reticular formation
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride
MSA	Multiple system atrophy
n-RS	RBD negative screened
PC	Precoeruleus
PD	Parkinson's Disease
PPN	Pedunculopontine nucleus
p-RS	RBD positive screened
PSG	Polysomnography

RBD	REM sleep behavior disorder
REM	Rapid eye movement
RWA	REM sleep without atonia
SLD	Sublaterodorsal nucleus
SN	Substantia nigra
SSRI	Selective serotonin reuptake inhibitor
vIPAG	Ventrolateral part of periaqueductal grey matter
VLST	Ventrolateral reticulospinal tract

INTRODUCTION

Parasomnias

Parasomnias are one of the major subdivisions of sleep disorders; this subset is characterized as defective behaviors taking place during sleep and/or the passage into or out of sleep. Within the class of parasomnias, there are 3 further subsets of disorders; categorized as disorders of arousal, disorders of rapid eye movement (REM) sleep or 'other'. Disorders of arousal arise when elements of wakefulness present in non-REM sleep; these include sleep terrors, confusional arousals, and sleepwalking. Disorders of REM sleep involve ailments of the REM stage of sleep, this area includes REM sleep behavior disorder (RBD) and nightmares. The most frequently encountered parasomnias in a clinical setting are sleepwalking, sleep terrors, confusional arousals, and REM sleep behavior disorder (Matwiyoff & Lee-Chiong, 2010).

REM sleep behavior disorder criteria and presentation

REM Sleep Behavior Disorder is a parasomnia affecting the REM stage of sleep, this disorder is marked by recurrent dream reenactment behaviors with superfluous motor activity resulting from a loss of typical muscle atonia (Claassen et al., 2010). A clinical feature of RBD is the presence of abnormal

vocalizations. These utterances are loud and suggest unpleasant dream content often manifested in shouting and screaming. Abnormal motor behavior is also noted; these motor behaviors are dramatic and appear to be purposeful activities while the patient is asleep. Additionally, RBD patients have altered dream mentation in which the patient is most often defending themselves in these unusually vivid dreams. It has also been noted that RBD patients do not forget the dream content rapidly upon waking, as non RBD patients would. Instead it is frequently noted that those with RBD recall the vividness and details of these dreams for days to years (Bradley F Boeve, 2010). Recent studies indicate 89% of the recalled dreams of RBD patients involve the patient facing aggression (Olson, Boeve, & Silber, 2000). This is a large contrast to a study conducted on 1,320 non-RBD dreams finding that only 34% involved malicious acts against the dreamer (Hall, 1951).

The International Classification of Sleep Disorders (ICSD)-2 produced by the American Academy of Sleep Medicine (AASM) requires the following for diagnosis of RBD (“International Classification of Sleep Disorders (ICSD-2) - American Academy of Sleep Medicine (AASM),” n.d.):

- 1) Existence of REM sleep without atonia, given by elevated electromyography (EMG) tone or extreme burst-like(phasic) muscle tone in the limb EMG readings of polysomnography (PSG) testing.
- 2) At least 1 of the following:

- a) Sleep related injury, or risk of sleep related injury associated behaviors via history.
 - b) Atypical REM sleep activity as documented on PSG testing.
- 3) Lack of epilepsy resembling behavior during REM sleep, unless RBD can be obviously isolated from any coexisting sleep-related seizure disorder.
- 4) These sleep disturbances cannot be better attributed to another disorder, medication use, or substance use.

RBD epidemiology and history

In humans, REM sleep becomes evident between the 27th and 30th week of gestation. During childhood REM sleep achieves a stable pattern that persists through adulthood (Schenck, Bundlie, Ettinger, & Mahowald, 1986). Each sleep cycle lasts approximately 90 minutes, each of these cycles containing between 20-30 minutes of REM sleep; thereby in a given night there will be 4 or 5 periods of REM sleep. Most slow wave sleep occurs during the first half of the night. During the second half of the night there is an increasing amount of stage two of sleep and bouts of REM sleep (Carlson & Carlson, 2011). As a result of REM sleep occurring more frequently later in the sleep cycle, so too are RBD symptoms and presentation seen during this time.

REM sleep behavior disorder was first detailed in cat models in the 1960's. However, Most of our initial knowledge on RBD comes from a study conducted by Schenck and colleagues on 5 elderly RBD patients in 1986; this was the first research outlining RBD in a human model (Aurora et al., 2010). All 5 of these subjects underwent PSG and neurological testing. Clinical histories were also taken, during which 2 out of the 5 patients reported the RBD episodes never occurring within 1 hour of falling asleep. Patients were videotaped while sleeping as a part of the PSG. Motions such as hand movements, reaching and searching behaviors as well as punches and kicks were observed in all participants and were found to be congruent with dream recall in all 5 participants. After analysis of the PSG data, Schenck et al. found all of the patients to exhibit phasic and desynchronized EEG waves during all REM periods recorded (Schenck et al., 1986). These are abnormal patterns, atypical of typical REM sleep in healthy subjects.

Four of Schenck's five participants were male, mirroring the predominance that is found towards males in the RBD population (Schenck et al., 1986). The overall prevalence of RBD in the general population is reported to be 0.5% (Matwiyoff & Lee-Chiong, 2010). Recent research by Olson et al. has found 87% of RBD sufferers are male, emphasizing the gender bias often reported in this condition. In the same study it was noted that out of 93 cases 32% had injured themselves during their RBD bouts, while 64% had assaulted their bed partners

(Olson et al., 2000). This is a great concern in the treatment and management of RBD patients as well as in ensuring their quality of life as many RBD patients find themselves unable able to share sleeping quarters with their partners.

Most frequently, RBD presents between ages 40 and 70. Rarely, RBD may develop in the teens or late 20's, however, this is more typically associated with narcolepsy (Bradley F Boeve, 2010). The tendency for RBD to arise late in life varies from the other non-REM disorders of arousal; many of the other parasomnias present much earlier. Additionally, RBD effects a much greater portion of men whereas non-REM disorders are found equally in both sexes (Matwiyoff & Lee-Chiong, 2010). This gender disparity however is much less pronounced in cases of early-onset RBD; here men account for only 55-59% of sufferers. RBD is considered to be early onset when it presents before age 50 (Ju, 2013).

Polysomnography and REM sleep behavior disorder

While not always feasible, polysomnography testing is critical in the diagnosis of RBD and is part of the required criteria for ICSD-2 diagnosis (Bradley F Boeve, 2010). When used for the detection of RBD, PSGs involve numerous EMG recordings including leads to all limbs and the chin. These EMG recordings are utilized to detect atypical muscle activity. Electroencephalogram

(EEG) recordings are taken to monitor brain waves as a means to determine sleep stages and abnormalities in these stages and the transitions between them. Participants' body temperatures are also noted as these will rise as the patient enters REM sleep. Additionally, PSG often records video during the night so night time behaviors may be observed and compared temporally with PSG data (Kunz & Mahlberg, 2010). REM sleep stage is defined via PSG by low amplitude mixed frequency EEG background, rapid eye movements, and low chin EMG tone. REM sleep without atonia (RWA) may be determined when there is continuous muscle activity in REM sleep with 50% of the REM period showing increased EMG activity in the chin. RWA is also characterized by abundant and brief muscle activity. To be considered RWA, this transient muscle activity must present 5 or more times in an epoch, each of these epochs must extend at least 0.5 seconds (Bradley F Boeve, 2010). While the loss of atonia is required for RBD diagnosis, it alone is not sufficient to produce RBD behavior (Schenck et al., 1986).

During RBD episodes patients may show muscle activity that is either tonic (sustained activity lasting 20-30 seconds) or phasic (burst-like lasting between 2-3 seconds) on EMG recordings (Verhave et al., 2011). Variations in limb activity have been observed between men and women. Studies have observed women to have more arm movements whereas men tend to exhibit more leg movement. This underscores the important of EMG placement on all

limbs (Trotti, 2010).

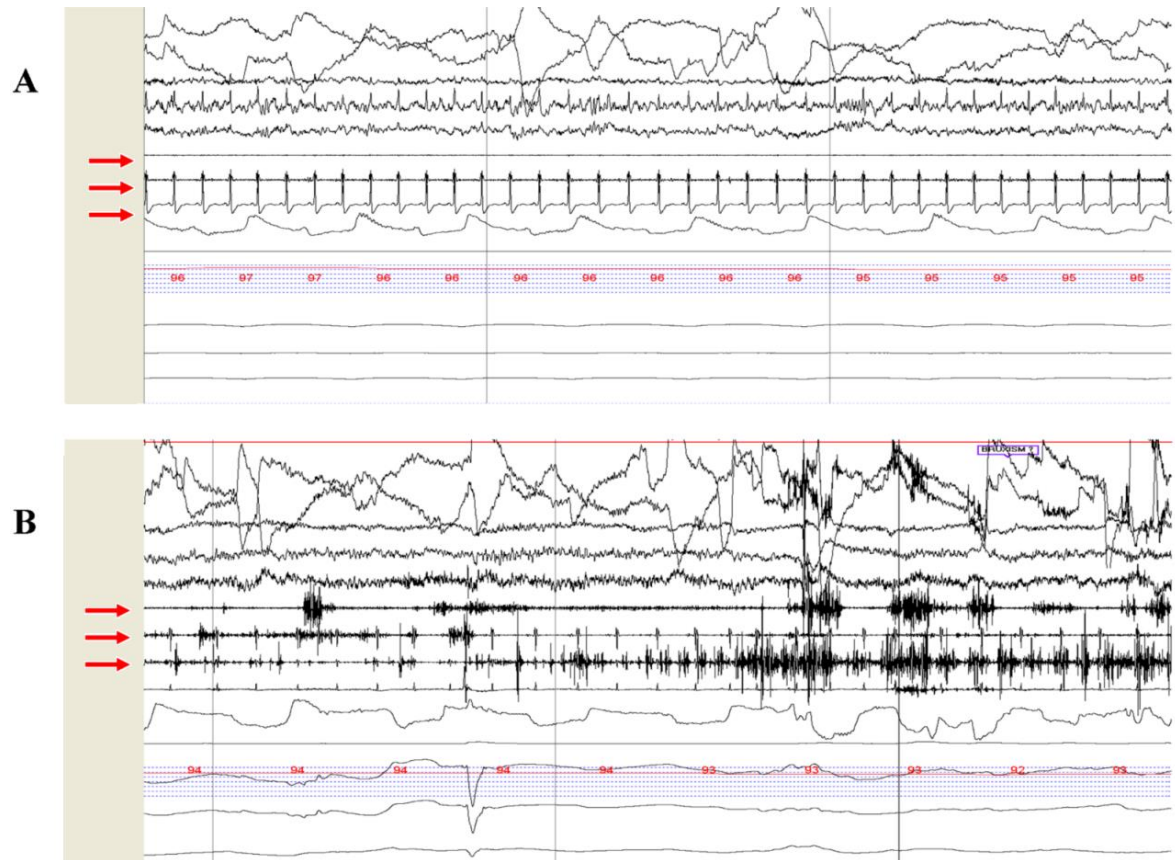


Figure 1. PSG recording of control and RBD case. Two thirty second period polysomnograms showing normal REM sleep (A) and REM sleep without atonia (B), a feature of RBD. In A, note the absence of EMG activity beside the three arrows, depicting the activity found in the Chin, upper, and lower limbs. The same muscle groups are noted in B by arrows, here abundant muscle tone is noted as evidence of the loss of muscle atonia. Figure annotated from Bradley F. Boeve 2010.

Pathophysiology of RBD

While the neurological pathways responsible for REM sleep and RBD are not well understood, there are many hypotheses regarding the nuclei involved. Few post-mortem pathology studies have been conducted on human RBD patients with no other known neurological disorders. The two best currently understood animal models for RBD pathology are the cat and the rat (B F Boeve, Dickson, et al., 2007).

Research on the cat model of RBD pathology advocates for two motor systems being involved in typical REM sleep; one of which ensures muscle atonia while the other suppresses locomotor activity. In this paradigm, the absence of motor activity typically found in normal REM sleep is due to inhibition of spinal motor neurons and a reduction in the drive of generating nuclei. The brain areas most studied for their effects on RBD in the cat model are the magnocellular reticular formation (MCRF), locus coeruleus, pedunculopontine nucleus (PPN), laterodorsal tegmental nucleus (LDTN), and the substantia nigra (SN). The MCRF functions to hyperpolarize, and thereby inhibit, anterior horn cells in the spinal column through projections of the ventrolateral reticulospinal tract (VLST). Lesions experimentally produced in the MCRF release the tonic inhibition on these spinal motor neurons, leading to RWA behaviors. Similarly, lesions to the locus coeruleus, a nuclei located in the pons, results in RWA.

Interestingly, the size and extent of lesions in this area determines if complex behaviors are elicited during the RWA episodes (B F Boeve, Silber, et al., 2007).

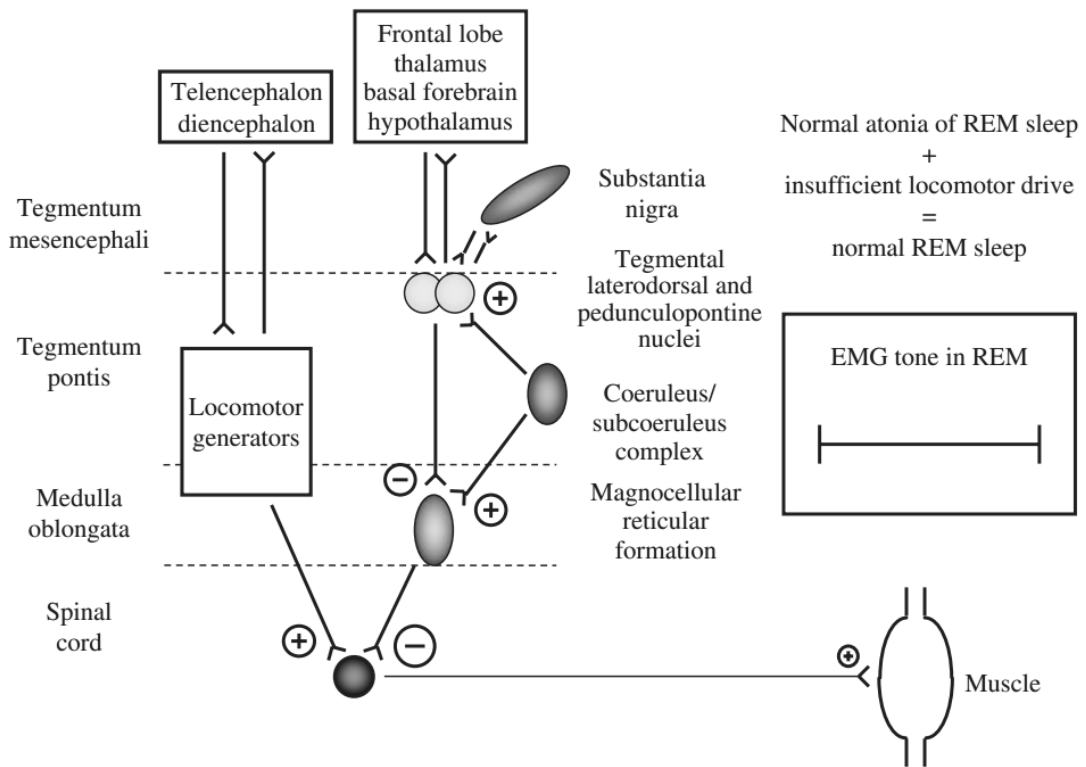


Figure 2. Proposed REM sleep modulation in the cat model. Each oval represents a distinct nuclei. Excitatory synapses are represented by plus signs, inhibitory synapses are noted by minus signs; the size of each of these symbols denotes the relative intensity of each synapse. This figure shows the proposed REM sleep pathways described in the text. Figure annotated from B.F. Boeve Silber et al. 2007.

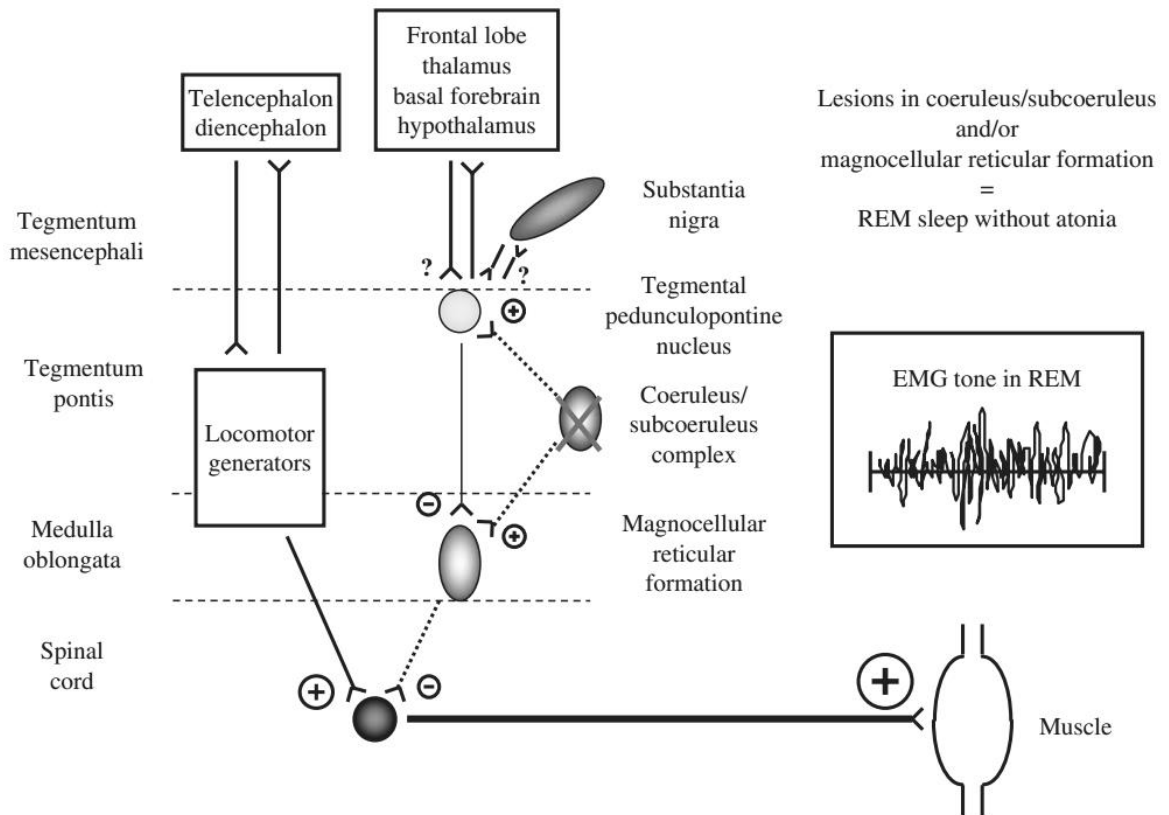


Figure 3. Model for pathophysiology of RWA based on cat model. Each oval represents a distinct nuclei. Excitatory synapses are demonstrated with plus signs, inhibitory synapses with minus signs. The relative size of these symbols represents the magnitude of their effects. A cross out through an oval/nuclei represents an experimentally produced lesion. Relative tonic influences are represented by line thickness; thicker lines yield stronger influences while dotted lines represent the weakest due to damage. This representation shows the pathways by which lesions to certain brainstem nuclei, namely the Locus Coeruleus, may result in RWA. Figure annotated from B.F. Boeve Silber et al. 2007.

The other leading model for RWA and RBD pathology is the rat model. In the rat, the sublaterodorsal nucleus has been determined to be comparable to the subcoeruleus region in the cat and found to be a major REM sleep structure. In the rat model an area known as the REM-off region resides in the ventrolateral part of the periaqueductal grey matter (vIPAG) and lateral pontine tegmentum (LPT). This area is responsible for turning off the REM phase of sleep and perpetuating progression through the rest of the sleep cycle. Lesions in these areas will result in an increase in the amount of REM sleep experienced. These neurons are hyperpolarized by GABAergic (gamma-aminobutyric acid) projections from the forebrain and depolarized by projections from the Locus Coeruleus and pathways of the lateral hypothalamus (B F Boeve, Silber, et al., 2007).

The REM-on region in the rat resides in the sublaterodorsal nucleus (SLD) and precoeruleus (PC) regions. These neurons have reciprocal interactions with the REM-off area and are mutually inhibitory. The rat SLD projects to the medulla and spinal cord where it will inhibit anterior horn motor neurons, as seen in the cat model, and inhibit motor activity during REM sleep. Thereby it is proposed that lesions to the SLD leads to disinhibition of spinal motor neurons resulting in RWA (B F Boeve, Silber, et al., 2007).

Treatment Options

REM sleep behavior disorder treatment is largely symptomatic and most frequently recommended when there is a risk of injury or sleep disturbance to the patient or their bed partner. The two most frequently used treatments are clonazepam and exogenous melatonin. More often, clonazepam is used as a first line of treatment while melatonin is used as a second method (Trotti, 2010).

Clonazepam is a long acting benzodiazepine with a half-life of 30-40 hours and is rapidly absorbed after oral administration. Recommended doses range from .25mg- 2mg typically 30 minutes prior to bed. It has been noted that women may require a higher dose (Aurora et al., 2010). Clonazepam has been found to suppress atypical motor symptoms without restoring REM atonia (Trotti, 2010). The mechanism by which clonazepam works is through binding to benzodiazepine alpha receptors to promote GABAergic inhibition; this increased inhibition results in a reduced REM percentage while having little effect on muscle atonia (McCarter et al., 2013). In doing so, clonazepam reduces phasic muscle activity in REM sleep and improves the main features of RBD while still allowing RWA to be observed on PSG testing (Bradley F Boeve, 2010).

The use of clonazepam to treat RBD comes with side effects such as daytime sleepiness, muscle relaxation in the elderly, reduced sleep quality,

cognitive impairment or worsening of sleep apnea (Kunz & Mahlberg, 2010). Considering these side effects, clonazepam should be used with discretion in patients with obstructive sleep apnea, gait disorders or dementia. A recent study found 58% of 36 patients on clonazepam had moderate to severe side effects while taking this medication, leading to a significant rate of discontinuation. Failure to take clonazepam results in a rapid reoccurrence of RBD symptoms. However, discontinuation of clonazepam does not result in withdrawal symptoms and tolerance has not been observed. Despite the prevalence of side effects, larger studies have reported that more than 80% of patients improve while taking clonazepam (Aurora et al., 2010). Additionally, a study conducted in Hong Kong found the rate of sleep related injury as a result of RBD behavior decreased from 80.8% pre-treatment to 5.6% after treatment with clonazepam (Wing et al., 2008).

While melatonin is not as widely studied as clonazepam, it still offers a beneficial treatment for many patients (Aurora et al., 2010). Melatonin is believed to decrease the percent of REM sleep epochs without muscle atonia and decrease the stage shifts within REM sleep (Bradley F Boeve, 2010). A recent review of clinical practices investigated two retrospective case series which included a total of 38 RBD patients, 81.5% of which reported improvement on melatonin. The same clinical review found a significant decrease in the number of RWA epochs detected via PSG (Aurora et al., 2010), leading current research

to believe melatonin may help restore muscle atonia during REM sleep (McCarter et al., 2013). The mechanism by which melatonin is believed to decrease RBD symptoms is not well understood, but is currently believed to involve GABAergic inhibition and stabilization of circadian rhythm that often becomes misaligned in RBD. Melatonin may act to re-train the suprachiasmatic nucleus to help restore circadian modulation (McCarter et al., 2013).

In healthy subjects, melatonin has been shown to increase the duration of the first REM episode of the night. In a small randomized study of 8 RBD patients by Kunz and Mahlberg, 87% of patients reported improvement in RBD symptoms and many reported decreased daytime sleepiness. These improvements were still felt after a washout period where the participants were asked to refrain from taking melatonin. Participants reported improvement lasting for 5 weeks after discontinuation; indicating that melatonin has long lasting effects after administration. Additionally, Kunz and Mahlberg's subjects reported a resolution of clinical RBD lasting up to 3 years after discontinuation of melatonin (Kunz & Mahlberg, 2010).

Synucleinopathies

Between 38% and 65% of patients with idiopathic RBD (iRBD) followed longitudinally are found to develop an alpha synucleinopathy between 10 to 29

years after presentation of RBD (Aurora et al., 2010). This category of disorders is distinguished by the presence of Lewy bodies (LB) and Lewy neuritis (LN)- which are pathological aggregations of alpha synuclein (McKeith, 2005). Parkinson's disease (PD), Dementia with Lewy bodies(DLB) and Multiple System Atrophy(MSA) all share the similarity of alpha synuclein positive intracellular inclusions, leading to these disorders to be jointly recognized as the synucleinopathies (B F Boeve, Silber, et al., 2007)

In cases of non-synucleinopathies, RBD occurs at the onset of, or after the presentation of the motor and cognitive features of the neurodegenerative disease. The information that RBD is more frequent in alpha-synucleinopathies indicates that despite Parkinson's disease and neural degeneration, there are likely to be other abnormalities in the brain stem that result in the difference between syn and non-synucleinopathies (B F Boeve, Silber, et al., 2007). RBD appears to occur frequently in the synucleinopathies likely as a result of susceptibility in critical brain stem nuclei involved in RBD pathology being consistent with those involved in synucleinopathy pathology (Bradley F Boeve, 2010).

Neuronal degeneration in PD and DLB is thought to initiate in the central nervous system and go on to impact peripheral neurons (Kaufmann, Nahm, Purohit, & Wolfe, 2004). The core features of DLB include fluctuation, visual

hallucinations and Parkinsonism. Progressive debilitating cognitive impairment is a requirement for the diagnosis of DLB (McKeith, 2005). In nearly every case of DLB there is pathology present in the brainstem, in the later stages the Lewy bodies are established in cortical areas of the brain (McKeith, 2005) (Dickson, Uchikado, Fujishiro, & Tsuboi, 2010). PD is believed to begin with alpha-synuclein depositing in the medulla initially then progressing to rostral areas. This progression may explain RBD preceding Parkinsonism and cognitive decline (Bradley F Boeve, 2010).

Braak Staging System of Lewy Body Pathology

Anatomical region	Braak PD stage	Kosaka LBD types
Anterior olfactory nucleus Dorsal motor nucleus of vagus	1	(Not assessed) Brainstem
Locus ceruleus Substantia nigra	2 3	Transitional
Basal nucleus of Meynert Amygdala	4	
Parahippocampal and cingulate limbic cortices	5	Diffuse
Multimodal association cortices of temporal, frontal, and parietal lobes	6	
Primary motor and visual cortices		

Table 1: Summary of two staging systems for the distribution of Lewy Bodies in Parkinson's Disease. This table shows the brain areas thought to be affected by PD and Lewy body pathology temporally. This representation clearly shows that the nuclei thought to be involved in RBD including the locus coeruleus and substantia nigra, are among those affected in the earliest stages of PD. Table taken from Dickson et al., 2010

Recent studies have shown 70% of MSA patients, 40% of DLB patients, and 15-33% of PD patients present with comorbid RBD (Aurora et al., 2010). The Blonogna, Genova, Parma, and Pisa universities group for the study of RBD in PD used a questionnaire of 200 PD patients to reveal that 34% of their PD patients had suggestive histories of RBD (Scaglione et al., 2005). Most specialists in this discipline are beginning to view patients presenting RBD concurrently with cognitive impairment and/or parkinsonism as likely having an underlying synucleinopathy (Bradley F Boeve, 2010).

The data available on the topic of the RBD alpha-synucleinopathy relationship is very limited due to the lack of follow up over an extended period of time (Terzaghi et al., 2008). While literature is abundant on the subject, most of the studies and data are low level with small sample sizes (Aurora et al., 2010). . It is evident that RBD has a high prevalence in this population and may be able to serve as a pre-clinical risk factor and diagnostic measure in the detection of alpha-synucleinopathies. Further study of the correlation between RBD and synucleinopathies may allow for earlier and more accurate diagnosis, thereby possibly having implications in the treatment of these neurodegenerative disorders.

Specific Aims and Objectives

The objective of the present study is to investigate the correlation between REM sleep behavior disorder and the many aspects of alpha-synucleinopathies.

Specifically:

1. To identify the presence of screening practices for RBD in movement disorders patients.
2. To examine the prevalence of RBD in our population that was screened for RBD and to stratify this by type of synucleinopathy.
3. To examine what methods they were treated with and if improvements were noted among patients with at least one follow up visit.
4. To investigate the incidence of sleep related injuries to the patient and their bed partner.

METHODS

This study was conducted by means of an internal review board approved retrospective chart review and analysis of 300 Boston Medical Center patients. These patient charts were obtained through the movement disorder outpatient clinic at Boston Medical Center and were all diagnosed with synucleinopathy from September 2006 through September 2011.

The charts were reviewed and relevant data was placed in a Microsoft Excel spread sheet. All data was obtained through reading clinical notes written by the treating physician. Data recorded included, but is not limited to, age, sex, synucleinopathy diagnosis, duration of synucleinopathy- for PD patients the severity of their disease was noted in the form of a Hoehn and Yahr (HY) scale scoring. The HY score was obtained by either their physician noting their score in the charts, or by us assessing the patient retrospectively from their most recent notes to determine what their HY score is likely to be given information noted in their chart. It was noted if the clinician screened for the presence of RBD via PSG or questions, RBD presence was then noted. Whether the patient was being treated for the RBD and what their treatment consisted of was recorded. Information regarding personal injury and injuries to sleeping partners as a result of RBD were noted. All medications for treatment of the synucleinopathy were noted as well as the time of each dosage. Other current medication information

was recorded. All medications were recorded from the most recent treatment plans noted in their charts.

There was no contact with the participants while obtaining data for this study. All patient identities were kept confidential via use of medical record numbers rather than personal identifiers. There were no exclusion criteria for our cohort. The participants were not compensated for their participation.

Statistical analysis included finding averages, standard deviations, and ranges of data collected. Correlational statistics included Wilcoxon sign tests, t-tests, and regression analysis. These were computed by means of Microsoft excel, SPSS 21 and STATA.

RESULTS

Out of our sample size of 300, 79 (26.3%) were not screened for RBD by their physician. As a result, these participants were neither confirmed nor ruled out of RBD presence, their results were not used in any of the statistical analyses of significance for RBD correlations. As a result, the adjusted sample size of screened patients was 221.

Synucleinopathy prevalence in the population:

73.3 % (163) of our screened participants held a diagnosis of PD. Of these, 36.8 % (60) had comorbid RBD. Seventy-nine out of the total 229 PD patients reviewed were not screened for RBD. A total of 8.1 % (18) of our screened participants had DLB, and 61% (11) of those were experiencing RBD. Three DLB participants were not screened for RBD, amounting to 21 DLB charts having been reviewed. 6 MSA charts were reviewed. 1.3 % (3) of our screened participants held a diagnosis of MSA, 66% of those had RBD as well. 3 MSA participants were not screened for RBD by their providers. 51 charts with the diagnosis of Parkinsonism, a nonspecific synucleinopathy with Parkinson-like symptoms, were reviewed. 17.6 % (39) of our screened participants had Parkinsonism, of these 17.9% (7) also had RBD. Thirteen Parkinsonism participants were documented as being unscreened for RBD.

	Total	Screened	Screened with RBD	Screened no RBD	Unscreened
PD	229	163	60	103	63
MSA	6	3	2	1	3
DLB	21	18	11	7	3
Parkinsonism	51	39	7	32	13
Dual Diagnosis	7	-	-	-	-

Table 2. Patients over each synucleinopathy and screening. This table demonstrates our participant numbers in regards to synucleinopathy diagnosis, RBD presence, and the presence of screening.

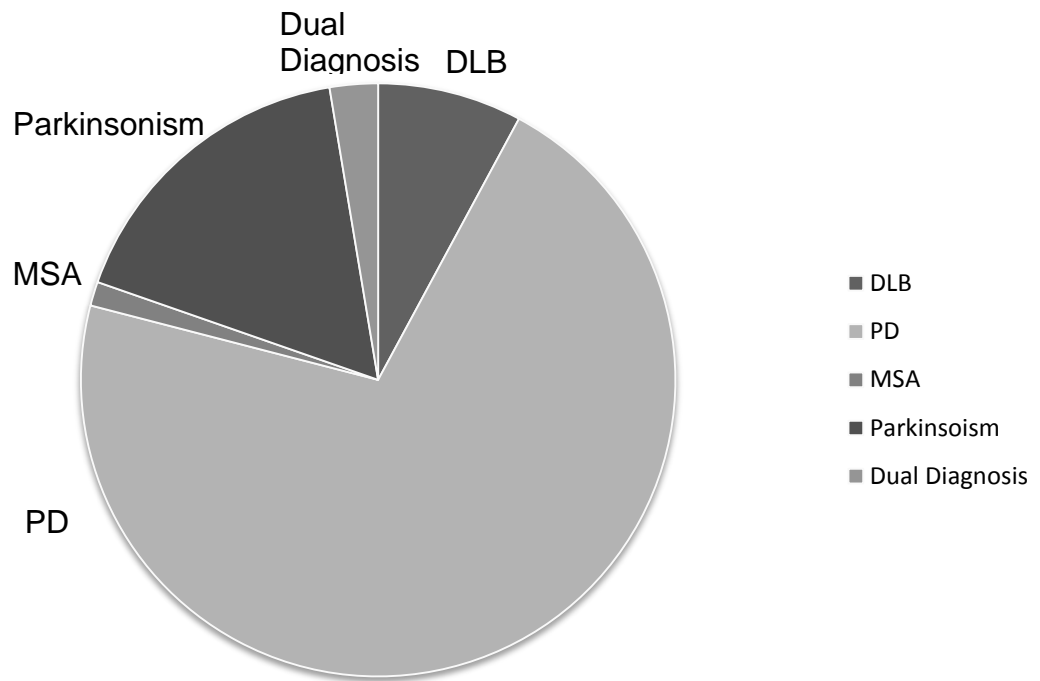


Figure 4. Frequencies of each synucleinopathy in RBD screened participants. Of our screened population, DLB consisted of 8.1 %, PD 73.3%, MSA 1.3 %, Parkinsonism 17.6%, and 2.7 % had a dual diagnosis of more than one synucleinopathy.

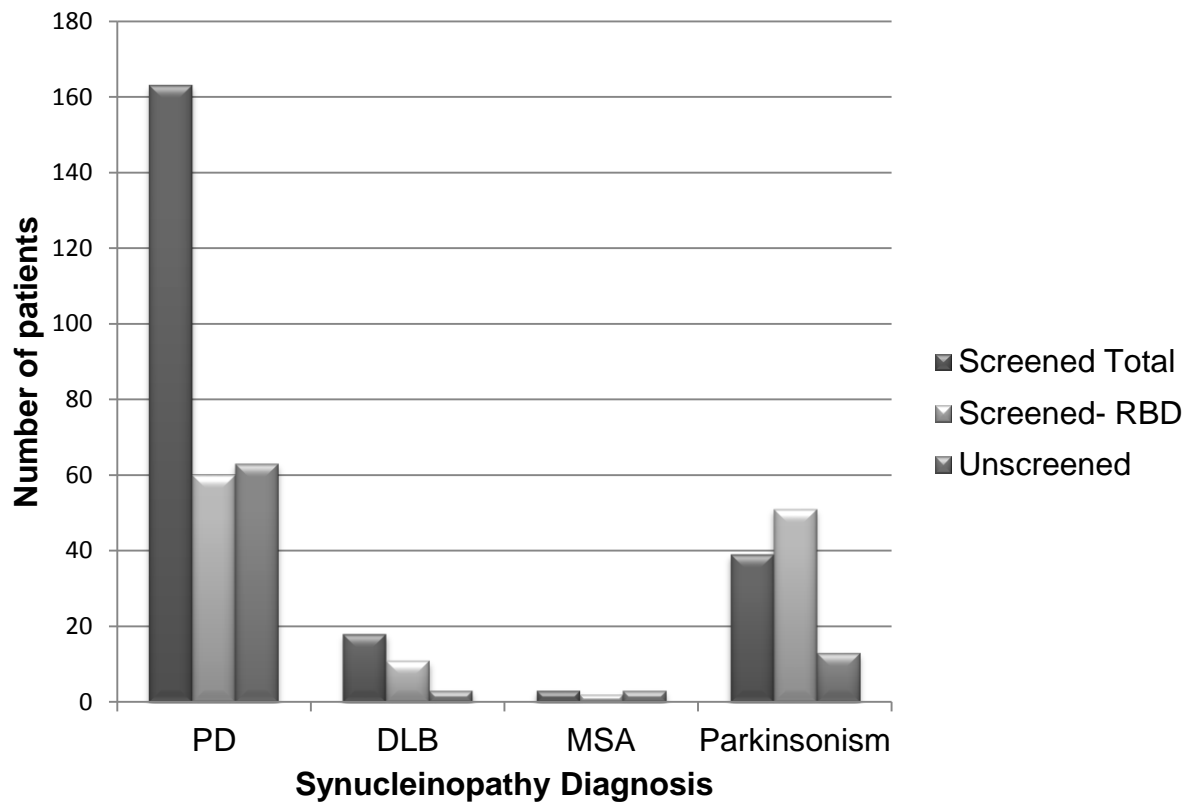


Figure 5. Comparison of screening and RBD diagnosis within each synucleinopathy. This figure graphically depicts the differences in population sizes, screening as well as RBD presence among the diagnoses. The bar furthest left in each section represents the total number of screened participants in each diagnosis. The middle bar of each represents the amount of those screened who were comorbid for RBD. The bar furthest right in each diagnoses shows the frequency of unscreened participants for that synucleinopathy.

Descriptive statistics of the RBD-negative screened (n-RS), RBD-positive screened (p-RS), and non-screened groups:

The n-RS group consisted of 140 participants. 79 participants were un-screened and 79 participants were screened and found to have RBD. The average age of the n-RS group was 71.6 years. The p-RS group had an average age of 70.9 years. The unscreened group had an average age of 72.4 years. The difference in ages between these three groups was not statistically significant by means of an independent samples T-test method of analysis.

H&Y scores:

The average H&Y score, a scale of PD symptomology, of PD patients within the n-RS group was 2.79. The average H&Y score of PD patients within the p-RS group was 3.06. An average H&Y score of 2.81 was found for the non-screened participants whom had PD. H&Y score was not found to be a significant predictor of RBD presence or the absence of screening when analyzed using a logistic regression method ($P = .14$).

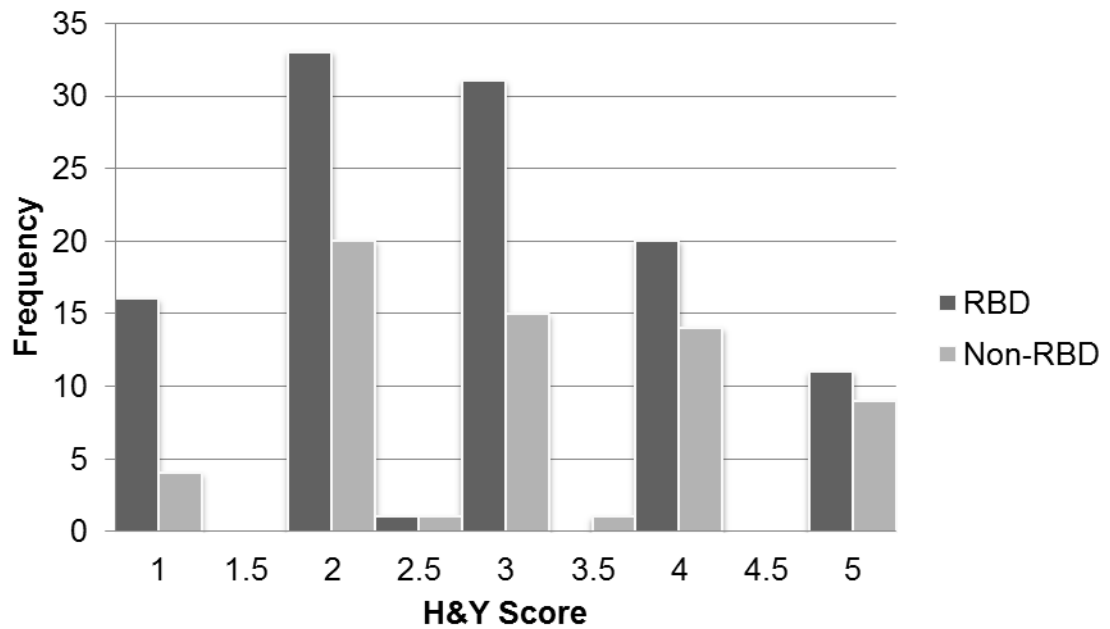


Figure 6. Frequency of H&Y scores for screened non-RBD and RBD participants. This figure graphically demonstrates the distribution and frequency of H&Y scores for participants with RBD and those without RBD. The distribution is fairly similar between the two groups, with most participants having a H&Y score of 2 or 3.

24% of the patients who were positive for RBD had charts that contained reports of partner complaints. 5% of RBD positive patients reported sleep related injuries as a result of their RBD. H&Y scores were not found to predict the likelihood of sustaining a sleep related injury in RBD-positive patients.

Synucleinopathy Duration:

The n-RS group of participants had average synucleinopathy duration of 7.13 years. The p-RS group had an average synucleinopathy duration of 8.17 years. The non-screened group was found to have an average synucleinopathy duration of 8.3 years. The duration of synucleinopathy was not found to significantly correlate to RBD presence or screening presence by means of a two-sample Wilcoxon rank-sum (Mann-Whitney) test ($P=.49$).

RBD treatment methods:

Of the 79 RBD patients, 46.8% were treated for their RBD. Of those treated, 62% were treated with Clonazepam on a range of .25-1mg with an average dose of .5mg \pm .16mg. A large proportion of treated patients (56.5%) reported improvements to their physicians which were documented in their charts. Melatonin was used to treat 37.8% of the RBD patients undergoing therapy, this method had a range of doses from 3-6mg with an average of 3.5mg \pm 1.1mg and, 57.1% of these participants reported improvements. Other medications such as remeron were used to treat 2.7% of our participants, these reported 100% improvement. The difference in improvement seen between those on melatonin and those taking Clonazepam was not found to be significant.

Gender differences:

Of our total population, 57.3% of participants were male while 42.7% were female. In our study, 46.7% of our screened participants who were not exhibiting RBD were male. In contrast, 72.2% of our RBD population was male. In our population, gender was found to have a statistically significant correlation with RBD presence by means of a logistic regression analysis ($P < .000$).

Selective Serotonin Reuptake Inhibitor (SSRI) Usage:

SSRI usage was reported in 24.2% of n-RS participants and in 32.9% of p-RS patients.

DISCUSSION

This study explored the relationship between RBD and alpha-synucleinopathies in order to identify RBD groups most at risk for developing synucleinopathies and to determine what treatments may provide the best therapy for this population.

In recent studies, 38- 65% of iRBD patients were reported to later develop a synucleinopathy when followed prospectively. Related studies show 15-33% of PD patients were comorbid for RBD (Aurora et al., 2010). Our study found 36.8% of our PD population was comorbid for RBD. This figure is closely in line with those obtained by other researchers, although at the higher end of the spectrum. Research conducted by other groups found that 70% of MSA patients also suffered from RBD (Aurora et al., 2010). Our study found 66% to be comorbid for RBD. These are very similar figures, which is especially interesting given this study only had 3 MSA patients who were screened for RBD. While our retrospective analysis was unable to report on the temporal relationship of RBD with synucleinopathy, a recent study reported 87.8% of their MSA patients having RBD, of those 30% reported the RBD beginning before their MSA presented and 63% reporting their RBD presenting after their MSA diagnosis (De Cock et al., 2011). This information serves as perhaps a sign of differing brain pathology in MSA compared to that of the other synucleinopathies. However, even with such

a small population of MSA patients our figure for RBD prevalence in this population is very similar to that of other studies.

The Journal of Sleep Medicine has previously reported 40% of DLB patients having been documented as suffering from RBD (Aurora et al., 2010). In our DLB population, 61% were screened and found to be exhibiting RBD. This is a somewhat larger number than previously reported studies. It is possible that the providers in the movement disorders clinic from which these charts were pulled are more aware of the RBD correlation in DLB and may be more diligent in exploring its presence in their patients than physicians in other clinics.

Despite some studies indicating that PD patients with clinical RBD have more severe Parkinsonism symptoms than those without RBD; In our study, Hoehn and Yahr scores were not found to correlate with RBD presence (Nomura, Inoue, Kagimura, & Nakashima, 2012). A higher Hoehn and Yahr score, which describes a more progressed PD symptomology, was not found to be indicative of an increased likelihood of being comorbid of RBD. This may be because the H&Y score is a scale only of symptom presentation- this score changes with medication and treatment. Patients may initially present with a H&Y score of 4, but after appropriate treatment their PD may progress back to a score of 2, indicating a less symptomatic stage than their initial presentation. As a result, scores fluctuate with medication compliance and treatment. H&Y scores used for

this study were noted as being the most recent in the participant's chart.

Additionally, the H&Y scale is not indicative of brain degeneration and the Braak and Braak stages of PD pathology (Burke, Dauer, & Vonsattel, 2008). However, since RBD often presents decades before the clinical presentation of synucleinopathies, it is likely that the Braak and Braak stage would be at most a 1 at the time of first RBD presentation given the time and lack of synucleinopathy symptomology (Claassen et al., 2010).

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP) is a drug that destroys specifically targeted dopaminergic neurons of the substantia nigra. This drug has been found to experimentally mimic the degeneration pattern of PD. MPTP administration in marmosets have produced in RBD- (as well as PD), and have allowed for dissection and analysis of brain degeneration in primates. This model hypothesizes that the degeneration process of PD is initiated in the medulla, then progress to the pons where it goes on to target the mid-brain. Thereby, the presence of RBD may indicate early involvement of non-dopaminergic medullary or pontine REM related structures. These REM related structures are closely connected to the substantia nigra and its pathways. As a result the REM related structures are likely affected by the dopamine imbalance caused by the early administration of MPTP, or early progression of PD (Verhave et al., 2011). Significant damage to the substantia nigra is not noted till Braak and Braak stage 3 (Dickson et al., 2010). Therefore, small early changes in

dopaminergic neurons may lead to effects in REM sleep many years ahead of PD presentation.

In our patient population, 36 % of our screened participants were found to have RBD as well as a synucleinopathy. Of those, 46.8% were treated for their RBD. 62% were treated on clonazepam and 37.8% were treated with melatonin. Clonazepam is commonly accepted as the most widely used form of treatment for RBD, so this treatment disparity is not surprising. 56.5% of our clonazepam patients reported improvements, while 57.1% of our melatonin patients reported improvement. In similar studies 80% of patients reported improvements on clonazepam and 81% reported improvements on melatonin (Aurora et al., 2010). It is interesting to note that in both, our study and that done by Aurora et al., the difference in improvement between melatonin and clonazepam patients is minimal. Both appear to be equally effective. It is possible our improvement results are lower due to reasons including physicians not recording this improvement in the patients' charts, increasing cognitive decline being an issue in judging the effectiveness via the patients self-report, or it may be due to a lack of patient follow-up.

Interestingly, only 46.8% of our RBD patient population was treated for their RBD. This information implies that it is often acceptable to not treat this condition. By the time they came into the movement disorders clinic from which

these patients' charts' were pulled. Many patients were already sleeping separately from their partners. Additionally, unlike other studies, our population all had movement disorders; perhaps this characteristic impaired their ability to fully exhibit RBD flailing movements and thereby posed less of a risk to bed partners. Our RBD population reported having sustained sleep related injuries (5%), and 24% reported partner complaints. A study conducted on RBD in Hong Kong found 80% of RBD patients had injured themselves during an RBD episode (Wing et al., 2008). Our patient population had substantially fewer reports of sleep related injuries, which may be a result of their movement disorder impairing their movements during RBD and thereby making treatment of the RBD less imperative.

The side effects of medication may also have contributed to fewer patients being treated for RBD. Clonazepam is known to have side effects including gait instability and clouded cognition (Aurora et al., 2010). These side effects may prove to be too great of a risk in a patient population that is already prone to gait instability and suffers from cognitive decline as a result of their synucleinopathy. The RBD episodes in our population may also be deemed too infrequent to warrant treatment. It is also possible that RBD may spontaneously resolve in our population, thereby lessening the need for treatment.

SSRI's are currently being evaluated for their potential to unmask or

potentially result in RBD symptomology. This association is strong; however it appears more often in early-onset cases. It has been long reported that SSRI usage in narcoleptic patients induced excessive motor activities in the REM sleep stage. Studies have explored this correlation regarding SSRI's between early and late onset RBD. In early onset cases, these studies found 80% and 57% of RBD patients to be on SSRIs. In late onset cases 46% and 38% of RBD participants were found to be taking SSRIs. Among all individuals in the general population taking SSRIs, 5% report RBD behaviors. Studies show SSRI usage among parasomnia sufferers to be higher than that found in the general population (Ju, 2013). In our study, 24.2% of our screened population who was not found to be suffering from RBD was on an SSRI. Meanwhile, 32.9% of our RBD group was found to be on SSRIs. Our rate of SSRI usage in RBD patients is somewhat less than reported by other studies. This may be a result of prescribing practices of the physicians in the movement disorders clinic from which these charts were pulled. It also may be a result of side effects in conjunction with their movement disorders making the use of SSRIs less desirable. It is also possible that our participants are so far progressed in their disease that SSRIs would no longer have an effect on RBD presentation, and that the SSRI correlation is largely a phenomena of early onset RBD and cases long before the presentation of synucleinopathy.

In RBD populations there is a commonly reported gender disparity. In late

onset IRBD (idiopathic REM sleep behavior disorder) is found to be much more prevalent in men than it is in women. In early onset iRBD, men and women are equally likely to present (McCarter et al., 2013). 87% of RBD sufferers were reported to be male in a recent study of 93 patients in a sleep clinic (Olson et al., 2000). In our population, 46.7% of our screened participants who were not exhibiting RBD were male. In contrast, 72.2% of our RBD population was male. While this number is still large, it is noticeably smaller than other reports on the gender disparity. This may be a function of the gender bias being a sign of increased sensitivity in males to RBD presentation that may decrease with disease progression. Most studies on RBD are conducted prospectively from sleep labs. Our study was completed retrospectively from a movement disorders clinic; this may explain why our gender imbalance was less than that of other studies. If males are more likely to display RBD earlier it would be logical for them to be more prevalent in studies that are designed prospectively beginning in a sleep clinic. Additionally, females may not report their RBD as frequently as men. It is possible that the excessive motor actions of females may be of less disturbance than that typically exhibited by men, and are thereby brought up to medical providers less frequently.

Our RBD patients had an average age of 70.9 years, the average age of RBD diagnosis is in the 60's or 70's with a frequent 4-5 year period until the patient is formally diagnosed with the condition (Trotti, 2010). This study was

unable to make note of the age of RBD onset, due to the nature of retrospective analysis and missing data. Our RBD patients presented with an average synucleinopathy duration of 8.17 years. It is possible to imagine many of our participants might have had their RBD begin in their 50's given the approximately 5 years it takes on average to recognize RBD, the duration of the synucleinopathy, and the often long time between RBD presentation and synucleinopathy diagnosis. RBD cases presenting before the age of 50 are considered to be early onset, and tend to have a smaller gender disparity (Ju, 2013).

Few studies have been conducted regarding RBD screening practices, particularly those used in the synucleinopathy population. 25% of our participants had no documentation of screening in their charts. This may be the result of either non-report by the physician, or a lack of screening.

Limitations:

This study was a retrospective analysis via chart reviews. As a result, we were only able to assess data provided by healthcare providers by means of patient charts. Many points of data were therefore missing, such as time of RBD onset, melatonin doses, and screening practices. By doing a retrospective review it is difficult to conclude temporal relationships between factors.

Our study was also subject to a selection and regional bias. While this was a limitation, it was also a unique feature of our study. Most studies on RBD are conducted on patients referred to a sleep center. In our study, the participants were taken from a movement disorders clinic. As a result, our synucleinopathy patients were likely further along in their disease than those normally studied by prospective means. Additionally, 100% of our participants were already diagnosed with a synucleinopathy- a correlation many studies explore prospectively.

Future Directions:

Future studies should be done to further explore the effectiveness of melatonin and clonazepam in the synucleinopathy population; given the uniqueness of their degeneration other therapeutics may prove to be more beneficial. Additionally, more research should be done on whether it is advantageous to treat RBD in this population or if it is indeed acceptable to pursue non-treatment of RBD in synucleinopathy populations.

The gender bias in synucleinopathy patients presenting with RBD is also an area warranting more research. More studies should be done to explore if this disparity diminishes with the progression of the synucleinopathies. By pursuing a

better understanding of the gender bias it may be possible to better identify those at risk for developing a synucleinopathy and perhaps aid in finding better early detection methods for females.

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