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Understanding the Relationship between Non-motor Symptoms of Parkinson's
Disease and Sleep Disorders

A dissertation submitted in partial satisfaction of the requirements for the degree
Doctor of Philosophy

in

Clinical Psychology

by

Ariel B. Neikrug

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2014

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Chair

University of California, San Diego

San Diego State University

2014

DEDICATION

To my loving parents who empowered me to always pursue my dreams and
taught me the value of living life inquisitively and fully

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FIELDS OF STUDY

Major Field: Clinical Psychology

Behavioral Medicine and Health Psychology

Behavioral Sleep Medicine

ABSTRACT OF THE DISSERTATION

Understanding the Relationship between Non-motor Symptoms of Parkinson's
Disease and Sleep Disorders

by

Ariel B. Neikrug

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2014
San Diego State University, 2014

Professor Sonia Ancoli-Israel, Chair

Non-motor symptoms (NMS) are common in Parkinson's disease (PD) and are considered the most disturbing symptoms to both patients and caregivers. Sleep disorders including rapid-eye-movement sleep behavior disorder (RBD), obstructive sleep apnea (OSA), restless legs syndrome (RLS), and periodic limb movement in sleep (PLMS) are common in and contribute to the disability of PD patients. This study evaluated the impact of sleep disorders on the NMS of PD.

Eighty-six PD patients were evaluated and assessed for sleep disorders, sleepiness and the multiple NMS of PD. Principal component analyses and hierarchical multiple regression analyses were used to assess the relationship between the different NMS and the existence of sleep disorders.

Results showed that sleep disorders are significant contributors to NMS in PD ($p<0.001$) with age ($p=0.011$), dopaminergic therapy ($p=0.013$), RBD ($p=0.008$), and RLS ($p=0.013$) as significant predictors of the NMS score. Additionally, having sleep disorders (i.e., RBD, RLS, OSA) significantly predicted reported nighttime sleep dysfunction ($p<0.001$), poor mood ($p=0.002$), increased fatigue ($p=0.001$), and reduced quality of life ($p<0.001$). However, having a sleep disorder did not significantly predict subjective or objective daytime sleepiness.

In summary, this study showed that in the PD patient population, the presence of co-morbid sleep disorders predicts more NMS symptoms in general. More specifically, having sleep disorders (i.e., RBD, RLS, OSA) predicted increased reports of nighttime sleep dysfunction, poor mood, lower quality of life, and increased fatigue in this sample of PD patients. Of the sleep disorders assessed in this study, RBD and RLS were indicators of increased NMS but OSA was not. Further studies are now necessary to indicate if treatment of these sleep disorders will result in improved NMS and improved quality of life for PD patients and their caregivers.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily characterized by motor symptoms and increasing motor-related disability, including bradykinesia, rigidity, and tremor (Olanow, Stern, & Sethi, 2009). PD is the second most common neurodegenerative disease after Alzheimer's disease with over one million people affected in the United States. The prevalence of PD increases with age with rates estimated at 1% of adults over the age of 50 and 4% of adults over the age of 80 (de Lau & Breteler, 2006). As a result of the aging population in the United States, it is expected that the number of PD cases will double by 2030 (Dorsey et al., 2006).

The clinical manifestation of PD dramatically differs between individuals. In a study that followed 136 PD patients over 10 years, manifestation varied at follow-up from no functional disability to extreme disability of wheelchair or bed-bound (Hely et al., 1999). The presentation of non-motor symptoms (NMS) in PD also drastically differ (e.g., cognition/dementia, depression, and sleep impairment) and our understanding of such heterogeneity in PD is limited and incomplete (Hughes et al., 2000; Chaudhuri, Healy, & Schapira, 2006).

Non-Motor Symptoms in PD

While motor dysfunction is the hallmark symptom of PD, this disease is also strongly associated with NMS which have a major negative impact on the lives of patients, their families, and caregivers. NMS in PD include, among others, depression, cognition, daytime sleepiness, and sleep disturbances (Findley et al.,

2002). Chaudhuri et al. (2006) suggested that NMS dominate the clinical reality of PD patients and contribute to the severe disability these patients experience, impair quality of life, and even shorten life expectancy. In a large multicenter study of 1072 PD patients, NMS were reported by 99% (Barone et al., 2009). Other studies have suggested that the NMS carry more significance than motor symptoms when assessing caregiver distress, institutionalization rates, quality of life, and overall economics of PD (Chaudhuri et al., 2006; Findley et al., 2003; Findley et al., 2002). A 15-year follow-up study of PD patients reported that the NMS which did not respond to dopamine therapy (e.g., dementia, sleep disruption) were “more disabling than end-of-dose failure or dyskinesia” and were the major cause of morbidity and mortality (Hely, Morris, Reid, & Trafficante, 2005). Of the NMS in PD, depression and sleep dysfunction have also been recognized as prodromal features and predictors of cognitive impairment and reduced quality of life (Santamaria, Tolosa, & Valles, 1986). Furthermore, NMS are often not reported, poorly recognized and inadequately treated (Chaudhuri et al., 2006; Chaudhuri et al., 2010; Shulman, Taback, Rabinstein, & Weiner, 2002). One study reported that neurologists failed to identify NMS (i.e., depression, sleepiness, and sleep disturbances) in up to 75% of PD patients (Shulman et al., 2002).

Depression

Depression is common in PD and is thought to affect about 40% of this population, nearly twice that is expected in other, equally disabled, populations (Cummings & Masterman, 1999; Reijnders, Ehrt, Weber, Aarsland, & Leentjens,

2008). However, as diagnostic criteria used widely vary between studies, the exact prevalence is questionable with reports ranging between 3-80% (Marsh, McDonald, Cummings, & Ravina, 2006; Cummings & Masterman, 1999; Schwarz et al., 2011; Farabaugh et al., 2011). Furthermore, depression is both under-diagnosed and undertreated in PD (Cummings & Masterman, 1999; Shulman et al., 2002), likely in part because PD and depressive illnesses share several common features including psychomotor slowing, loss of interest, trouble sleeping, poor concentration, poor appetite, and fatigue (Schwarz et al., 2011; Reiff et al., 2011; Leentjens & Verhey, 2002; Marsh et al., 2006). The etiology underlying this connection between PD and depression is not completely clear but is likely to be multi-factorial including reactive (e.g., adjustment to the disease) and organic causes such as the neurodegenerative process of PD and other neurochemical changes in the dopamine, noradrenaline and serotonin pathways (Cummings & Masterman, 1999; Tandberg, Larsen, Aarsland, Laake, & Cummings, 1997; Remy, Doder, Lees, Turjanski, & Brooks, 2005). Depression has also been recognized as a predictor of early development of PD (Farabaugh et al., 2011; Cummings & Masterman, 1999). Studies assessing depression in PD have demonstrated a relationship to disease severity, motor disability, memory difficulties, sleep disturbances, and overall quality of life (Dissanayaka et al., 2011; Reiff et al., 2011).

Cognition

Contrary to early assumptions that cognitive dysfunction was not an essential feature of PD, it has become increasingly apparent that patients with PD have increased risk of developing dementia (Marder, Tang, Cote, Stern, & Mayeux, 1995; Reid, Hely, Morris, Loy, & Halliday, 2011). Cognitive dysfunction in patients with PD can range from domain-specific cognitive impairments to severe deficits which are extensive enough to fulfill criteria for the diagnosis of dementia. Neuropsychological investigations of PD patients show that specific cognitive changes, especially attention and executive function deficits, occur early in the course of PD and may be related to disruption of frontostriatal circuits (Lees & Smith, 1983; Collerton, Burn, McKeith, & O'Brien, 2003). A recent examination of the neuropsychological performances of clinically diagnosed Alzheimer's disease versus PD found that patients with PD performed significantly worse on attention-related tasks and better on memory tests than Alzheimer's disease patients (Noe et al., 2004).

The exact pathophysiology of cognitive dysfunction in PD is uncertain although a number of neurochemical and neuropathological changes are thought to be involved. Loss of cholinergic, dopaminergic, and noradrenergic innervation are thought to be the neurochemical deficits that underlie cognitive impairment and dementia in PD. Cognitive dysfunction and dementia have been reported to adversely affect both the quality of life in patients with PD as well as that of their

spouses and family members (Aarsland, Larsen, Karlsen, Lim, & Tandberg, 1999; Schrag, Jahanshahi, & Quinn, 2000).

Excessive daytime sleepiness

Excessive daytime sleepiness is one of the most widespread and disturbing non-motor symptom of PD with estimates as high as 74-81% of PD patients affected (Garcia-Borreguero, Larrosa, & Bravo, 2003; Chaudhuri et al., 2002; Rye, Bliwise, Dihenia, & Gurecki, 2000; Schapira, 2004). In fact, researchers suggested a narcolepsy-like pathophysiology of sleep-wake disturbances in PD (Arnulf et al., 2002). Several studies reported that excessive daytime sleepiness is one of the main risk factors for sleep attacks in PD (Paus et al., 2003; Hobson et al., 2002; Roth et al., 2003; Brodsky, Godbold, Roth, & Olanow, 2003). A large epidemiological study of over 6,600 PD patients reported that 60% were still driving and that 15% of those still driving were involved in a traffic accident in the previous five years (Meindorfner et al., 2005). While not necessary linked to excessive daytime sleepiness, this study did also report that PD patients with more severe excessive daytime sleepiness were more likely to have caused an accident.

The etiology of excessive daytime sleepiness is not clearly understood. Several studies identified the use of dopaminergic drugs as a possible cause of excessive daytime sleepiness in PD (Happe & Berger, 2001; Kaynaka, Kiziltana, Kaynaka, Benbira, & Uysalb, 2005; Andreu et al., 1999; Ferreira et al., 2006; Brodsky et al., 2003). However, other studies have suggested that excessive daytime sleepiness is independent of these sedating medications (Trenkwalder,

2005; Ondo et al., 2001; Roth et al., 2003; Stevens, Cormella, & Stepanski, 2004; Gjerstad, Alves, Wentzel-Larsen, Aarsland, & larsen, 2006; Gomez-Esteban et al., 2006). Previous research showed that, in demented older adults without PD, decreased exposure time to bright light during the day was associated with poor sleep and circadian desynchronization, which may contribute to excessive daytime sleepiness (Shochat, Martin, Marler, & Ancoli-Israel, 2000). Excessive daytime sleepiness is also a main consequence of some sleep disorders, particularly obstructive sleep apnea (OSA). However, studies that assessed excessive daytime sleepiness and OSA in PD patients failed to find this relationship (Cohen De Cock et al., 2010; Arnulf et al., 2002). Such differing findings prompted researchers to agree that excessive daytime sleepiness in PD is a multifactorial phenomenon (Adler & Thorpy, 2005).

Sleep, Sleep Complaints, and Sleep Disorders in PD

Sixty to 98% of PD patients complain of sleep-related difficulties (Lees, Blackburn, & Campbell, 1988; Gjerstad, Wentzel-Larsen, Aarsland, & larsen, 2007; Chaudhuri et al., 2006). In a community-based study of sleep disorders in PD, 32% complained of difficulty falling asleep, 39% reported frequent awakening during the night, and 23% reported early morning awakenings (Tandberg, Larsen, & Karlsen, 1998). At an 8-year follow-up in a longitudinal study of nocturnal sleeping problems in PD, 23% reported of difficulty falling asleep, 44% reported difficulty staying asleep, and 20% reported early morning awakenings. Furthermore, 83% of the PD patients reported sleep complaints at one or more

visits during this 8-year study and such complaints were related to disease duration and depression (Gjerstad et al., 2007). A different study reported that sleep complaints significantly predicted poor health-related quality of life in PD (Karlsen, Tandberg, Arslan, & Larsen, 2000).

In general, sleep disturbances increase with age, however multiple studies report that PD patients experience greater sleep and circadian rhythm disruptions compared to age-matched controls (van Hilten et al., 1994; Happe et al., 2005; Whitehead, Davies, Playfer, & Turnbull, 2008; Stavitsky, Saurman, McNamara, & Cronin-Golomb, 2010; Tandberg et al., 1998; Dhawan et al., 2006). Studies utilizing polysomnography (PSG; overnight sleep recordings) reveal significant sleep fragmentation in PD including decreases in total sleep time and percent of stage 3 (N3, 'deep sleep') and increases in percent of stage 1 (N1) sleep (Bergonzi, Chiurulla, Gambi, Mennuni, & Pinto, 1975; Friedman, 1980; Lavie, Bental, Goshen, & Sharf, 1980; Mouret, 1975). Additionally, disease duration is reported to be associated with additional decreases in sleep efficiency (the percent of time asleep given the amount of time in bed), total sleep time, deep sleep, and rapid eye movement (REM) sleep time, and increases in sleep onset latency and daytime sleepiness (Diederich, Vaillant, Mancuso, Lyen, & Tiete, 2005; Ondo et al., 2001).

Sleep disruption in PD is likely due to a multitude of factors including the neurodegenerative process of the disease itself. PD is marked by dopamine dysfunction and degeneration of the dopaminergic neurons. Dopamine circuitry is also thought to be implicated in several major sleep disorders common in PD such

as insomnia and restless legs syndrome (RLS) (Nofzinger, 2006). There are reports suggesting that PD patients exhibit dopamine dysfunction in the hypothalamus, a key area in the regulation of sleep-wake which may contribute to symptoms of insomnia, circadian rhythm disruption, and daytime sleepiness (Politis, Piccini, Pavese, Koh, & Brooks, 2008). In addition, brain stem deterioration is reported in PD and is also implicated in the REM sleep processes such as muscle atonia during REM (Chaudhuri et al., 2006). Other factors may also be responsible for disturbed sleep in PD including the medications used to treat the PD, motor symptoms, pain, nocturia, and other sleep disorders common in this age group (Kaynaka et al., 2005; Garcia-Borreguero et al., 2003; Schenck, Bundlie, & Mahowald, 1996; Bliwise et al., 1995).

Obstructive sleep apnea (OSA)

OSA is characterized by respiratory abnormalities that include complete cessations (apneas) and/or partial decreases (hypopneas) of breathing during sleep. The prevalence of OSA in PD is estimated at 20-60% (Arnulf et al., 2002; Zoccolella et al., 2010; Norlinah et al., 2009; Maria et al., 2003; Cochen De Cock et al., 2010). The sleep fragmentation and accompanying hypoxemia in OSA lead to many negative consequences including cardiac arrhythmias, nocturnal hypertension, nighttime confusion and neuropsychological impairment (Ancoli-Israel & Coy, 1994; Shepard, 1992; Redline et al., 1997).

Symptoms of OSA include disturbed sleep, excessive daytime sleepiness, cognitive decline, and depression, all of which are also recognized as NMS of PD.

It has been reported that the severity of PD correlates with the severity of the OSA, with one study finding 12.2 respiratory events per hour of sleep in mild-moderate PD compared to 5.7 events in age-matched controls (Maria et al., 2003). A recent study reported that OSA does not correlate with excessive daytime sleepiness, nocturia and cognitive impairment in PD (Cochen De Cock et al., 2010). However, methods utilized in this study prevent generalization and application of these results. For example, half of the sample was selected for complaints of sleepiness and OSA had a significantly lower incident (27%) in this sample than would be expected (~50% similar to the prevalence of OSA in the general older adult population). Additionally, this study assessed excessive daytime sleepiness subjectively with non-PD specific measures, used the Mini-Mental State Examination to assess for overall cognition (a measure with questionable validity and reliability for this end in this population), assessed depression based on use of antidepressants, and did not include any quality of life measures.

Restless Legs Syndrome (RLS) and Periodic Limb Movement during Sleep (PLMS)

RLS is a disorder characterized by uncomfortable sensations in the legs usually in the evening during restful periods and is accompanied by the urge to move (Phillips, Hening, Britz, & Mannino, 2006). RLS diagnosis is based on history, specifically on the positive response to 4 criteria: urge to move legs associated with paresthesias, motor restlessness, temporary relief achieved with movement, and worsening at night (Walters et al., 1995). Up to 56% of PD

patients suffer from RLS (Oerlemans & de Weerd, 2002; Ondo, Vuong, & Jankovic, 2002; Braga-Neto, da Silva-Junior, Sueli Monte, de Bruin, & de Bruin, 2004), significantly more than expected in the general population (up to 10%) (Rothdach, Trenkwalder, Habersack, Keil, & Berger, 2000; Allen et al., 2005). However, there is a debate surrounding the etiological link between PD and RLS. Evidence for shared pathophysiology include the positive response to dopaminergic therapy that suggests underlying dysfunction in dopamine circuitry in both PD and RLS, evidence that nigrostriatal system dysfunction is involved in both, and evidence linking RLS to specific PD genetic mutation (Happé, Pirker, Klosch, Sauter, & Zeitlhofer, 2003; Peeraully & Tan, 2012; Unger, Stiasny-Kolster, & Oertel, 2010). However, RLS has been shown, in some RLS patients, to be strongly associated with iron deficiency states while PD has been associated with elevated iron levels. Further contributing to the debate are mixed findings in functional imaging studies and studies assessing the effect of deep brain stimulation on RLS and motor symptoms of PD (Peeraully & Tan, 2012; Unger et al., 2010). Nonetheless, RLS has been shown to significantly impact health related quality of life in other populations, but little is known about how RLS impacts quality of life or other NMS in PD (Happé et al., 2009).

PLMS is a sleep disorder closely related to RLS and is characterized by stereotypic, repetitive movement of the lower limbs (kicks) that occur during sleep and cause arousals and subsequent sleep disruption (Iber, Ancoli-Israel, Chesson, & Quan, 2007; Vetrugno, D'Angelo, & Montagna, 2007; Neikrug & Ancoli-Israel,

2010). The relationship between PLMS and sleep quality is controversial, with some studies showing high impact on PSG parameters (Rosenthal et al., 1984; Bastuji & Garcia-Larrea, 1999) and on subjective perception of sleep (Roehrs, Zorick, Sicklesteel, Wittig, & Roth, 1983; Gómez-Choco et al., 2007), whereas other studies reported no such relationships (Manconi et al., 2008a; Auger, Montplaisir, & Duquette, 2005; Youngstedt, Kripke, Klauber, Sepulveda, & Mason, 1998; Manconi et al., 2008b). Studies demonstrated that up to 30% of PD patients present with excessive leg kicks during the night (Chokroverty, 1996; Wetter, Collado-Seidel, Pollmacher, Yassouridis, & Trenkwalder, 2000). In fact, some studies reported that leg kicks during the night are more common in PD patients compared to healthy age-matched controls (Neikrug & Ancoli-Israel, 2012; Alshubaili, Ohaeri, Awadalla, & Mabrouk, 2008). However, other studies did not detect significant differences in prevalence of leg kicks in the PD population (Happe et al., 2001; Arnulf et al., 2002). A recent study in our laboratory showed an association between leg movement indices and greater PD symptom severity, more subjective sleep disturbance, and decreased quality of life. Nearly all the PD patients in this study showed poor sleep. However, there were no significant differences on PSG measures between PD patients with versus without excessive leg movements (Covassin et al., 2012). It is important to point out that the study by Covassin et al. assessed total leg movements and not leg movements with arousals which would be the indicator for the diagnosis of PLMS.

REM sleep behavior disorder (RBD)

RBD is a parasomnia first identified and described in 1986 in 5 older adults that exhibited abnormal muscle activity during REM sleep (Schenck, Bundlie, Ettinger, & Mahowald, 1986). REM sleep is normally characterized by minimal skeletal muscle activity i.e., muscle atonia, which manifests as low amplitude levels on the sub-mental electromyographic channel in PSG (Iber et al., 2007). RBD is characterized by REM sleep without atonia i.e., abnormal increase of muscle activity during REM sleep that evident by phasic and/or tonic muscle activity on the electromyographic channel. In RBD, activity during REM sleep ranges from excessive phasic muscle twitching to simple (e.g., talking/yelling, jerking of body) and complex (e.g., punching, arm flailing) behaviors which can (but not necessarily) result in vigorous and violent movements. These movements are usually associated with vivid dreams and may result in injuries to the patient or the bed partner (Schenck, Hurwitz, & Mahowald, 1993; American Academy of Sleep Medicine, 2005). This loss of muscle atonia is typically described by patients as “acting out” their dreams. However, not all RBD involves dream-enactment behaviors and not every occurrence of vivid dreams is RBD. Previous research reported that up to 35% of RBD patients are not aware of dream-enactment behaviors (Iranzo, Santamaria, & Tolosa, 2009).

The prevalence rate of RBD in the general population is estimated to be between 0.38–0.5% (Ohayon, Caulet, & Priest, 1997; Chiu et al., 2000). RBD has been shown to be significantly more prevalent in individuals with chronic

neurological diseases such as multi-system atrophy (Plazzi et al., 1997), progressive supranuclear palsy (Arnulf et al., 2005), narcolepsy (Schenck & Mahowald, 1992) and PD (Iranzo et al., 2009). A high percentage of idiopathic RBD patients eventually develop neurodegenerative disease (Schenck et al., 1996), and RBD has been recognized as a strong predictor of the development of synucleinopathies, including PD (Boeve, Silber, Ferman, Lucas, & Parisi, 2001). Studies which followed idiopathic RBD patients reported that up to 65% developed a neurodegenerative disease within an average of 7 to 13 years after RBD onset (Schenck et al., 1996; Schenck, Bundlie, & Mahowald, 2003; Iranzo, Molinuevo, & Santamaria, 2008).

Muscle atonia during REM sleep is the result of an interaction between multiple neuronal systems in the brain. Animal studies have demonstrated the involvement of structures in the brainstem (e.g., locus coeruleus-subcoeruleus complex, the raphe nucleus, and substantia nigra) and forebrain (e.g., hypothalamus, thalamus) (Gagnon, Postuma, Mazza, Doyon, & Montplaisir, 2006; Boeve et al., 2007). These structures have been conceptualized in two distinct motor systems that allow for normal REM sleep; one system responsible for generation of the muscle atonia and the other responsible for the suppression of locomotor activity (Boeve et al., 2007). Nonetheless, the exact nature of the interaction of these structures in the generation of muscle atonia is not fully understood and merits further study. It is hypothesized that dysfunction in one or

more of these pathways is responsible for loss of muscle atonia during REM sleep and the pathogenesis of RBD (Boeve et al., 2007).

While RBD has been reported to affect up to 58% of PD patients (Iranzo et al., 2009), only few studies have systematically assessed the relationship between RBD and PD symptom manifestation. Overall, these studies show that PD symptoms manifestation differs between patients with RBD versus no RBD. More specifically, studies show that PD patients with RBD are more commonly men, of older age, tend to have more visual hallucinations, have more falls, have longer disease duration, and tend to have more cognitive impairment (Arnulf et al., 2000; Nomura et al., 2003; Pacchetti et al., 2005; Gjerstad, Boeve, Wentzel-Larsen, Aarsland, & larsen, 2008; Postuma, Gagnon, Vendette, Charland, & Montplaisir, 2008a; Postuma, Gagnon, Vendette, Charland, & Montplaisir, 2008b; Sinforiani et al., 2006; Vendette et al., 2007; Sixel-Doring, Trautmann, Mollenhauer, & Trenkwalder, 2011; Bugalho, da Silva, & Neto, 2011). However, these studies have significant limitation as most use the minimal criteria for RBD diagnosis (i.e., history of dream enactment behavior with no objective assessment), use inadequate outcome measures or have restrictive samples. Additionally, there are contrasting reports between studies which are likely due to the different methodology employed and different RBD definitions used (Iranzo et al., 2009).

Summary

Sleep disturbances and sleep disorders are common and vexing problems in PD. Other NMS such as depression, sleepiness, and dementia are common in PD

and significantly impact quality of life of PD patients and their families. Sleep disorders can result in symptoms that closely resemble the NMS of PD. However, only few studies have attempted to tease out such relationships. The impact of sleep disorders on cognition, sleepiness, and quality of life in the general non-PD population is indisputable. However, few have systematically assessed this relationship in PD patients. In a review of sleep in PD, Adler and Thorpy (Adler & Thorpy, 2005) suggested that effective diagnosis and management of sleep disturbances might greatly improve the quality of life in these patients. Additionally, in a recent study on NMS in PD, Chaudhuri and Schapira (Chaudhuri et al., 2006) suggested that the recognition and quantification of NMS should form the basis of improved treatments, as some NMS, including sleep disturbances, can be improved with available treatments. This proposed study is designed to systematically assess the relationship between sleep, sleep disorders, and the NMS of PD.

Parts of this dissertation has been modified for publication and submitted. Written consent was provided by coauthors. The dissertation author was the primary author on these paper and will be cited as: Neikrug AB, Maglione JE, Liu L, Natajara L, Avanzino JA, Corey-Bloom J, Palmer B, Lored JS, and Ancoli-Israel S. Effects of sleep disorders on the non-motor symptoms of Parkinson disease.

STUDY AIMS

Aim 1

To assess the impact of sleep disorders (OSA, RBD, RLS, PLMS) on overall subjective reports of non-motor symptoms of Parkinson's disease including cognition, depression, sleep complaints, Subjective daytime sleepiness, functional impairment, and quality of life.

Hypothesis: Parkinson's disease patients with sleep disorders (OSA, RBD, RLS, PLMS) will experience overall more non-motor symptoms compared to those without sleep disorders.

Aim 2

To assess the relationship between objective daytime sleepiness, dopaminergic therapy, and sleep disorders (OSA, RBD, RLS, PLMS) in Parkinson's disease.

Hypothesis: Sleep disorders (OSA, RBD, RLS, PLMS) will account for greater amount of variance in daytime sleepiness when controlling for dopaminergic therapy.

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Avanzino JA, Corey-Bloom J, Palmer B, Lored JS, and Ancoli-Israel S. Effects of sleep disorders on the non-motor symptoms of Parkinson disease.

METHODS

This study utilized data from a larger study that evaluated the effect of continuous positive airway pressure therapy on OSA, sleep, sleepiness, and cognition in a sample of patients with PD and OSA. PD patients were referred by neurologists at the University of California, San Diego, by community neurologists in San Diego County or volunteered after hearing a talk about the study at Parkinson Disease support group meetings. Patients were excluded if they were receiving current treatment for OSA, had bronchospastic and symptomatic chronic obstructive pulmonary disease, coronary or cerebral vascular disease, active seizure disorder, any neurodegenerative disorder other than PD, receiving deep brain stimulation treatment for PD, had current alcohol or drug abuse, or any other physiological (e.g., incontinence) or psychological impairments that would have limited their participation. Patients were allowed to use their prescribed medications as long as they were stable on the same dose for two months prior to enrollment in the study and remained on the same dose throughout the study. The study was approved by the University of California, San Diego Human Research Protections program, San Diego Veterans Administration Healthcare System, and San Diego State University.

Parkinson's Disease Assessment

Parkinson's disease characteristics

The Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn, Elton, & UPDRS Program Members, 1987) was used to characterize the progression of PD

and was completed by a neurologist. The UPDRS consists of five subscales evaluating cognitive and emotional status (UPDRS I – mentation, behavior and mood; range 0-16), daily functioning (UPDRS II – activities of daily living; range 0-52), motor symptoms (UPDRS III – motor examination; range 0-108), and side effects of therapy (UPDRS IV – complications therapy; range 0-23). An overall score, as well as a score for each subscale, was computed with higher scores indicating more severe disease.

Parkinson's disease severity

Hoehn and Yahr Scale (H&Y) (Hoehn & Yahr, 1967) was utilized to assess PD severity. The H&Y was completed by a neurologist. The H&Y grades patients from stage 0 (no signs of disease) to stage 5 (wheelchair bound or bedridden unless assisted).

NMS Questionnaires:

Multiple symptoms evaluation

The Non-motor Symptoms Questionnaire (NMSQuest) (Chaudhuri et al., 2006) is a 30-item questionnaire completed by the patients. The NMSQuest allows a brief yet comprehensive assessment of the non-motor features of PD, including neuropsychiatric, sleep, autonomic, gastrointestinal, sensory and other disturbances. This scale was shown to have good psychometric properties and valid as an instrument for detecting NMS in PD (Chaudhuri & Martinez Martin, 2008).

Mood evaluation

Beck Depression Inventory- 2nd edition (BDI-II) (Beck, Steer, & Brown, 1996) was used to evaluate symptoms of depression and was completed by the patients. The BDI-II is well validated and is the most frequently used scale for depression (Beck, Steer, & Garbin, 1988; Richter, Werner, Heerlein, Kraus, & Sauer, 1998; Levin, Llabre, & Weiner, 1988). The BDI-II is composed of 21 questions that are related to depressive symptoms including hopelessness, irritability, crying, guilt, physical sensations, poor concentration, fatigue, appetite changes, and sleep. Answers are scored on a 0-3 scale (total score range 0-63) with higher total scores indicating greater depression. Visser, Leentjens, Marinus et al. (2006) evaluated the reliability and validity of the BDI-II in PD. Their series of studies showed good internal consistency (0.88), test-retest reliability (0.89), with good discriminant validity, and sensitivity to change and treatment. A study that validated sub-threshold depression in PD concluded that the BDI-II score 9 to 15 best differentiates sub-threshold depression in this population (Reiff et al., 2011). The use of the BDI-II in PD was championed by expert panels for monitoring severity of symptoms and for evaluation of therapeutic interventions (Schwarz et al., 2011).

Quality of life evaluation

Parkinson's Disease Questionnaire (PDQ-39) (Peto, Jenkinson, & Fitzpatrick, 1998) was designed and validated specifically for evaluating quality of life in PD. This measure was completed by the patients. The PDQ-39 has 39 items on mobility, emotional well-being, stigma, social support, cognitions,

communication and bodily discomfort. Results can be presented either as a profile or as a single index. In a review of different quality of life scales for patients with PD, Marinus, J. et al. (Marinus, Ramaker, van Hilten, & Stiggelbout, 2005) concluded that the PDQ-39 is the single most appropriate quality of life instrument for this population.

Cognition evaluation

The Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) is a brief screening tool designed to identify mild cognitive impairment. The MoCA was administered by trained study staff during consent. The MoCA is divided into 7 subscales: visuospatial/executive, naming, memory, attention, language, abstraction, and orientation. There are 30 available points with one additional point added for subjects with ≤ 12 years of education. The MoCA has been demonstrated to have good reliability and validity in PD (Gill, Freshman, Blender, & Ravina, 2008). MoCA has been shown to be more sensitive in detecting mild cognitive impairment than the Mini Mental State Exam in PD (Zadikoff et al., 2008).

Subjective daytime sleepiness evaluation

The Epworth Sleepiness Scale (ESS) (Johns, 1991) is a self-administered questionnaire in which subjects rate the likelihood of their falling asleep in different situations on a four level rating scale, including “would never do” to “slight, moderate or high chance of dosing”. Eight daytime situations are rated, such as sitting and reading, watching television, talking with someone, sitting in a car. The ESS has been shown to reliably distinguish good sleepers from those with

excessive daytime sleepiness disorders including obstructive sleep apnea, narcolepsy and idiopathic hypersomnolence.

Fatigue evaluation

The Short Form of the Multidimensional Fatigue Symptom Inventory (MFSI-SF) (Stein, Martin, Hann, & Jacobsen, 1998) is a short (30 questions) measure that was developed in cancer populations. The MFSI-SF provides a total fatigue score and five subscales: General, Physical, Emotional, Mental, and Vigor. Assessment of the MFSI-SF showed sound psychometric properties and a stable multidimensional factorial structure.

Subjective sleep evaluation

The Parkinson's Disease Sleep Scale (PDSS) (Chaudhuri et al., 2002; Chaudhuri & Martinez-Martin, 2004) is a self-administered questionnaire that is designed to assess sleep complaints and nocturnal difficulties that are more pertinent in PD. Items address overall quality of sleep, sleep onset and sleep maintenance insomnia, nocturnal restlessness, nocturnal psychosis, nocturia, nocturnal motor symptoms, sleep refreshment and daytime dozing. The PDSS has good discriminatory power between patients with PD and healthy controls. The severity of the symptom is marked on a 10cm line which is labeled best to worst. The responses are quantified by measuring the distance along each line. Scores for each of 15 items range from 0 (symptom severe and always present) to 10 (symptom free). The mean of the scales is computed, with lower scores suggesting more severe sleep disruption.

Subjective Clinical Sleep Evaluation

RBD evaluation

REM Behavior Disorder Sleep Questionnaire (RBDSQ) (Stiasny-Kolster et al., 2007) was administered by a physician specializing in sleep medicine. The RBDSQ was used to assess clinical history of dream enactment behavior. This screening tool for RBD is based on the clinical criteria of the International Classification of Sleep Disorders, second edition (American Academy of Sleep Medicine, 2005). It is composed of 10 yes/no items with maximum score of 13. The RBDSQ was previously validated with a cutoff score of 5 exhibiting 96% sensitivity and 56% specificity (Stiasny-Kolster et al., 2007). The Japanese version of this measure was recently validated for use in PD (Nomura, Inoue, Kagimura, Uemura, & Nakashima, 2011).

RLS evaluation.

A structured questionnaire was administered to diagnose RLS according to International Restless Legs Syndrome Study Group criteria (Miller, 2004). The RLS assessment was conducted by a physician specializing in sleep medicine. This questionnaire is composed of four questions assessing: 1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; 2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting; 3. The urge to move or unpleasant sensations are partially or totally relieved by movement, at least as long as the activity continues; 4. The urge to move or unpleasant sensations are worse in

the evening or night than during the day or only occur in the evening or night. All four criteria had to be satisfied for diagnosis of RLS.

Objective Clinical Sleep Evaluation

Sleep recording.

The first four participants had PSG recorded with Embla (Planegg, Germany). The remaining participants had PSG recorded with the video-enabled Compumedics Somté (Charlotte, NC). Electroencephalography (F4, C4, O1 or O2), electrooculography (left and right outer canthus), submental electromyography, respiratory effort (thoracic and abdominal piezoelectric bands), airflow (nasal pressure transducer), electrocardiogram, oximetry and tibialis electromyography were recorded. In addition, technicians noted any visible arousals (e.g., restroom visits, taking medication), any environmental changes (e.g., noise), any vocalization during sleep (e.g., yelling/talking), and any movements (e.g., kicking/arms flailing) both on the PSG recording and in a journal.

Sleep recordings were scored by a scorer blind to the clinical assessment, treatment condition, and questionnaire data. All PSG records were staged according to accepted American Academy of Sleep Medicine criteria (Iber et al., 2007). REM scoring allowed for REM-sleep without atonia. Apneas were scored when there was >90% decrease in airflow amplitude from baseline lasting for ≥ 10 seconds. Hypopneas were scored when there was 50-90% decrease in amplitude lasting ≥ 10 seconds, associated with an arousal or an oxygen desaturation $\geq 3\%$.

Apnea-hypopnea index (AHI; the number of apneas+hypopneas/hour of sleep) and periodic leg movement index (the number of leg kicks in a 5-90-seconds periodicity of ≥ 4 consecutive leg movements/hours of sleep) were computed.

RBD scoring.

To assess for RBD, submental electromyography was assessed for REM-sleep without atonia. Electromyography scoring utilized criteria that are nearly identical to the RBD PSG scoring method developed by Lapierre and Montplaisir (Lapierre & Montplaisir, 1992) and validated by Consens et al. (Consens et al., 2005) including computation of tonic and phasic components as defined by the American Academy of Sleep Medicine guidelines (Iber et al., 2007) with several minor differences: a) While the American Academy of Sleep Medicine guidelines recommend the use 30-second epochs divided into 10 sequential 3-second mini-epochs, the Somté software only allowed for 30-second epochs divided into 12 sequential 2.5-seconds mini-epochs; b) Each REM sleep epoch was scored either tonic or atonic. Whereas the American Academy of Sleep Medicine guidelines define a tonic epoch as a REM sleep epoch with $>50\%$ of the epoch's duration showing chin EMG amplitude greater than the minimum amplitude present in non-REM sleep, in this study, a tonic epoch was defined as a REM sleep epoch with $>50\%$ of the duration exhibiting an increase in chin Electromyography amplitude that was at least two-times the non-REM baseline. The phasic component was calculated as the proportion of REM sleep mini-epochs containing phasic activity. Phasic activity was defined as transient bursts of muscle activity 0.1–5.0 seconds

in duration and at least four-times the amplitude of background electromyography-activity. Using these criteria, a REM sleep epoch could contain 0 mini-epochs with phasic activity and still be considered tonic or, on the other hand, have 12 mini-epochs with phasic bursts and be atonic because the phasic bursts were not sustained for >50% of the epoch's duration.

An electromyography score (EMG-score) was calculated as the average of the percent of tonic REM sleep epochs and the percent of phasic REM sleep mini-epoch. The EMG-score is similar to the RBD measure previously proposed by Consens et al. (Consens et al., 2005) which established a cut-off score of 10% with a sensitivity of 89% and specificity of 57%.

Finally, patients will be diagnosed with RBD as suggested by the International Classification of Sleep Disorders, second edition (American Academy of Sleep Medicine, 2005). Current criteria of confirmed-RBD according to the International Classification of Sleep Disorders, second edition involves subjective clinical history with objective documentation of either REM-sleep without atonia or dream enactment behavior during an overnight PSG. Therefore, patients will be classified into 3 groups based on subjective (RBDSQ) and objective (EMG-score and clear evidence of REM-sleep without atonia as recorded during overnight PSG) measures; Group 1, Yes-RBD group ($RBDSQ \geq 5$ and $EMG\text{-score} \geq 10\%$ or clear evidence of REM-sleep without atonia as recorded during overnight PSG); Group 2, No-RBD group ($RBDSQ < 5$ and EMG-

score<10); and Group 3, Probable-RBD group (either RBDSQ ≥ 5 or EMG-score $\geq 10\%$).

Objective assessment of daytime sleepiness.

A multiple sleep latency test (MSLT) (Littner et al., 2005) was utilized to objectively assess daytime sleepiness. The MSLT was conducted the morning after an overnight PSG and the sleep recording sensors were left on the patients during the 4 “naps”. The patients were asked to go to bed and try to fall asleep at 8:00am, 10:00am, 12:00pm and 2:00pm. Sleep was monitored and sleep onset latency was calculated. This test is not an opportunity to nap but rather an opportunity to test how long it takes one to fall asleep at different times of the day, thus evaluating daytime sleepiness. The recent practice parameters papers published by the American Academy of Sleep Medicine confirmed that MSLT is appropriate to examine changes in daytime sleepiness following treatment intended to alter sleepiness (Littner et al., 2005). The mean sleep onset latency of the 4 naps was calculated (MSLT-SOL) and this was used in subsequent analyses.

Medications

All patients were assessed for medication use (type, dose, frequency, time of administration, reason for use, and duration of use). Dopaminergic therapy regimen highly differs between PD patients. Therefore, in order to allow comparisons among patients on different dopaminergic regimens, drug dosages were converted to Levodopa Dosage Equivalents (LDE). Amantadine, rasagiline

and selegiline were not included in this computation. The computational formula was (Hobson et al., 2002; Yadav & Bourdette, 2011):

$$LDE = (regular\ Levodopa\ dose \times 1) + (Levodopa\ CR\ dose \times 0.75) + (pramipexole\ dose \times 67) + (ropinirole\ dose \times 16.67) + [regular\ Levodopa\ dose + (Levodopa\ CR\ dose \times 0.75)] \times 0.25\ if\ taking\ entacapone].$$

In order to assess the individual impact of dopamine agonist and carbadopa/levodopa on objective daytime sleepiness (Aim 2), separate equivalency formulas were used following (Grosset K A & Drosset D G, 2006; Hobson et al., 2002):

$$Levodopa-only\ Equivalent = (regular\ Levodopa\ dose \times 1) + (Levodopa\ CR\ dose \times 0.75) + [regular\ Levodopa\ dose + (Levodopa\ CR\ dose \times 0.75)] \times 0.25\ if\ taking\ entacapone].$$

$$Dopamine\ Agonist\ Equivalent = 1\ mg\ pergolide = 1\ mg\ pramipexole = 5\ mg\ ropinirole$$

Procedures

All patients were screened by telephone. For those meeting inclusion criteria, the study was described in detail and signed informed consent was obtained. All enrolled participants were tested for cognitive performance by a research associate using the MoCA, were evaluated by a neurologist (using the H&Y and UPDRS), and were assessed by a physician trained in sleep medicine for sleep history, assessment of possible sleep disorders (including completion of the RBDSQ and RLS evaluation), overall medical condition, and medication use.

Additionally, all patients completed the self-administered questionnaire packet that included the ESS, PDSS, BDI-II, PDQ-39, NMSQuest, and the MFSI-SF. All patients were admitted to the General Clinical Research Center (now Clinical and Translational Research Institute) Gillin Laboratory for Sleep and Chronobiology for an overnight video-enabled PSG followed by an MSLT during the following day.

Analysis

Summary statistics (means, SDs, ranges, frequencies) were computed for all variables of interest. Outcome measures (i.e., questionnaires, sleep parameters) were tested for normality by the Shapiro-Wilks statistic and Q-Q plots. Identified outliers were checked for accuracy against the original data records. The skewness and kurtosis for each variable were divided by the standard error (z-score) and those variables with significant deviations ($z > 1.96$) in skewness or kurtosis were transformed. Analyses were computed both with the transformed and untransformed data. When results were different, the assumption was made that the statistical violation of normality impacted the results and the transformed values were used. If the results were not different untransformed values were used. Pearson's correlations were used to assess the relationship between the different NMS measures.

Analysis Aim 1.

Aim 1: To assess the impact of sleep disorders (OSA, RBD, RLS, PLMS) on overall subjective reports of non-motor symptoms of Parkinson's disease

including cognition, depression, sleep complaints, subjective daytime sleepiness, functional impairment, and quality of life.

Hypothesis: Parkinson's disease patients with sleep disorders (i.e., OSA, RBD, RLS, PLMS) will experience overall more non-motor symptoms compared to those without the given sleep disorders

Principal component analysis is a data reduction technique that was used to derive component/factor scores for the NMS of PD by factoring the relationships among multiple observed variables that are designed to assess different NMS in PD. Given that seven NMS variables are under consideration, to avoid multiple comparisons, principle component analysis was used to derive component/factor scores that will best describe the NMS of PD by distinguishing sets of variables with stronger relationships among multiple observed variables (e.g., mood, sleepiness, functional impairment, and quality of life) (Meyers, Gamst, & Guarino, 2006). The principle component analysis was conducted utilizing the correlation matrix with a varimax rotation to allow factors to be correlated as all NMS in PD likely share variance. The first principal component was derived, which by construction captures the maximum variability in the NMS variables.

Two separate principle component analyses were conducted. The first (NMS_Total) included all seven outcome variables for the NMS in PD: MoCA (cognition), BDI (mood), PDSS (subjective sleep), ESS (subjective daytime sleepiness), PDQ-39 (quality of life), MFSI-SF (fatigue), and the NMSQuest (multiple symptoms evaluation). However, as sleep related difficulties may bias

prospective analysis (assessing impact of sleep disorders on the NMS factor), a second and separate principle component analysis was conducted (NMS_NoSleep) in which sleep-related outcome variables (i.e., PDSS, MFSI-SF, and ESS) were excluded and only other non-sleep variables (i.e., MoCA, BDI, PDQ-39, and the NMSQuest) were included.

A hierarchical linear regression correlation was used to assess the relationship between the NMS factors (i.e., first principle component of each principle component analysis) and the presence of sleep disorders while controlling for age, disease severity, and dopaminergic therapy. Using regression analysis allows assessing for the unique effects of each explanatory variable (unique sleep disorders) while statistically controlling (partialing) the effects of the other explanatory variables in a single model, thus minimizing the likelihood of a Type I error (Cohen, 2003). Age, disease severity, and dopaminergic therapy were included in block 1 and the sleep disorders were included in block 2 to assess if the inclusion of sleep disorders into the model resulted in significant increases of variance explained in the NMS factors (ΔR^2 and ΔF statistic). A significant model showing a given sleep disorder as a significant predictor ($p < 0.05$) would serve as an omnibus test of any association between that sleep disorder and NMS variable and would suggest that further analysis of this relationship is appropriate. The sleep disorders were included into the model as categorical variables and were defined as follows:

OSA: yes-OSA ($AHI \geq 10$) and no-OSA ($AHI < 10$)

RBD: yes-RBD (RBDSQ $\geq$ 5 and EMG-score $\geq$ 10% or clear evidence of REM-sleep without atonia as recorded during overnight PSG), no-RBD (RBDSQ $<$ 5 and EMG-score $<$ 10), and probable-RBD (either RBDSQ $\geq$ 5 or EMG-score $\geq$ 10%).

RLS: yes-RLS (endorsed all 4 RLS questions) and no-RLS (endorsed $<$ 4 RLS Questions)

PLMS: yes-PLMS (PLMI $\geq$ 5) and no-PLMS (PLMI $<$ 5)

The hypothesis here is that the existence of a specific sleep disorder will result in more NMS of PD. Therefore the null hypothesis is that sleep disorders are not related to increase NMS in PD (H_0 : $\beta_{OSA} = \beta_{RBD} = \beta_{RLS} = \beta_{PLMS} = 0$; H_A : not H_0).

The restricted linear regression model is given as:

$$NMS\ factor = \beta_0 + \beta_1(age)_i + \beta_2(H\&Y)_i + \beta_3(LDE)_i + \varepsilon_i$$

The full linear regression model is given as:

$$NMS\ factor = \beta_0 + \beta_1(age)_i + \beta_2(H\&Y)_i + \beta_3(LDE)_i + \beta_4(OSA)_i + \beta_5(RBD)_i + \beta_6(RLS)_i + \beta_7(PLMS)_i + \varepsilon_i$$

Independent sample t-tests were utilized to assess the differences in the NMS Factor between PD patients with versus without a given sleep disorder and one way analysis of variance (ANOVA) was used to assess differences in NMS between RBD groups (i.e., yes-RBD, no-RBD, probable-RBD).

Sleep disorders were further evaluated for their effect on individual outcome variables. Individual hierarchical linear regression correlations were used to model the effect of the sleep disorders on the individual NMS measure while controlling for age, disease severity, and dopaminergic therapy. As seven different

outcome measures were tested and to protect from Type I error, significant models were established at $p < 0.007$ ($0.05/7$). A given sleep disorder that was identified as a significant predictor within these models was then assessed post-hoc for differences between those with vs. without that identified sleep disorder using independent sample t-tests for OSA, RLS and PLMS, and ANOVA for RBD. As these post-hoc analyses were exploratory in nature, no Type I error protection was utilized at this stage.

Analysis Aim 2.

Aim 2: To assess the relationship between objective daytime sleepiness, dopaminergic therapy, and sleep disorders (OSA, RBD, RLS, PLMS) in Parkinson's disease.

Hypothesis: Sleep disorders (OSA, RBD, RLS, PLMS) will account for greater amount of variance in objectively measured daytime sleepiness when controlling for dopaminergic therapy.

Pearson's correlations were used to assess the relationship between subjective (ESS) and objective (MSLT-SOL) sleepiness measures and dopaminergic therapy (i.e., dopamine agonist-only equivalence, carbadopa/levodopa-only equivalence, and overall dopaminergic therapy equivalence). Hierarchical multiple regression analysis was used to assess the relationship between sleep disorders, and objective daytime sleepiness while controlling for dopaminergic therapy, age, and PD severity. Dopaminergic therapy, age, and PD severity were included in block 1. Sleep disorders were included in

block 2 to assess if the inclusion of sleep disorders into the model resulted in significant increases of variance explained in the sleepiness score (ΔR^2 and ΔF statistic). Sleep disorders were defined identically to the definition used in Aim 1. Objective daytime sleepiness was measured by average sleep onset latency of the 4 sleep opportunities during the MSLT (MSLT-SOL).

The hypothesis here is that the existence of a specific sleep disorder will result in more excessive daytime sleepiness (i.e., lower values on mean MSLT sleep onset latency). Therefore the null hypothesis is that sleep disorders are not related excessive daytime sleepiness in PD ($H_0: \beta_{OSA} = \beta_{RBD} = \beta_{RLS} = \beta_{PLMS} = 0$; H_A : not H_0).

The restricted linear regression model is given as:

$$MSLT-SOL = \beta_0 + \beta_1(LDE)_i + \beta_2(age)_i + \beta_3(H\&Y)_i + \varepsilon_i$$

The full linear regression model is given as:

$$MSLT-SOL = \beta_0 + \beta_1(LDE)_i + \beta_2(age)_i + \beta_3(H\&Y)_i + \beta_4(OSA)_i + \beta_5(RBD)_i + \beta_6(RLS)_i + \beta_7(PLMS)_i + \varepsilon_i$$

To assess the impact of dopamine agonist and/or carbadopa/levodopa dosages, the regression analyses was then conducted replacing the overall dopaminergic therapy term (LDE) with the separate equivalents formulas for dopamine agonist and carbadopa/levodopa-only.

Independent sample t-tests were utilized to assess the differences in objective excessive daytime sleepiness between PD patients with versus without OSA, RLS, and PLMS. And an ANOVA was used to assess differences in

objective excessive daytime sleepiness between RBD groups (i.e., yes-RBD, no-RBD, probable-RBD).

Parts of this dissertation has been modified for publication and submitted. Written consent was provided by coauthors. The dissertation author was the primary author on these paper and will be cited as: Neikrug AB, Maglione JE, Liu L, Natajara L, Avanzino JA, Corey-Bloom J, Palmer B, Lored JS, and Ancoli-Israel S. Effects of sleep disorders on the non-motor symptoms of Parkinson disease.

RESULTS

Demographics and Sample Characteristics

A total of 86 PD patients (mean age=67.4±8.8 years; Range: 47-89, 29f) were included in this study (complete consort table is provided in Figure 1). The majority of participants were Caucasian, married, and had at minimum an undergraduate degree. Complete sample demographics are provided in Table 1. Complete medical and PD characteristics are provided in Table 2. The patients were diagnosed with PD for an average of 6.3 years. The majority of the patients (79%) were evaluated at stage I or II of PD according to the H&Y, and no patients had stage IV or V. The specific dopaminergic therapy (i.e., levodopa, carbadopa, dopamine agonist) widely differed between patients and only 6 participants were not receiving any dopaminergic therapy. Additionally, 28% of the patients were receiving an antidepressant.

All 86 PD patients underwent a complete overnight PSG. Sleep variables are summarized in Table 3. On average, patients slept for 5 hours and 48 minutes during the overnight recording with overall poor sleep efficiency (SE, time asleep over time in bed = 74%). On average, patients had 7.1 arousals per hour of sleep, had a mean AHI of 14.1 and had 7% of sleep time spent below 90% O₂ saturation. Finally, periodic limb movement index for the sample was considerably high (periodic limb movement index =21.0).

Sleep disorders were diagnosed according to established criteria. Of the total sample, 45% (n=39) were diagnosed with OSA, 42% with RBD (n=36), and

22% (n=19) with RLS. Only 2 patients (2%) were diagnosed with PLMS and due to this small number this variable was removed from further analyses. Sleep variables by sleep disorder are provided in Tables 4a, 4b, and 4c.

Aim 1 Results: Sleep Disorders and Subjective NMS of PD

Of the seven outcome measures [MoCA (cognition), BDI (mood), PDSS (subjective sleep), ESS (subjective daytime sleepiness), PDQ-39 (quality of life), MFSI-SF (fatigue), and the NMSQuest (multiple symptoms evaluation)], only the BDI-II and MoCA violated normality assumption and thus were appropriately transformed for subsequent analyses. Measurement descriptives for the entire sample is provided in Table 5a, by OSA in Table 5b, for RBD in Table 5c, and for RLS in Table 5d. Correlations between the measures are provided in Table 6.

Principle component analysis

Principle component analysis on the seven NMS outcome measures included in this study resulted in a single component extracted (NMS_Total) that explained 54% of the variance (Eigenvalue=3.78). Each of the remaining components had an Eigenvalue less than 1.0 and explained 14% or less of the variability in the set of NMS variables. Examining the extracted weights for each variable revealed that most of the variable loaded heavily ($>|0.8|$) on this component with only subjective sleepiness (0.48) and cognition (-0.27) not heavily loading on this component.

Omitting the sleep-related variables (i.e., ESS, PDSS, and MFSI-SF) the second principle component analysis also resulted in a single component extracted

(NMS_NoSleep) that explained 58% of the variance (Eigenvalue=2.33). Each of the remaining components on this PCA had an Eigenvalue less than 1.0 and explained 24% or less of the variability in this set of variables. Only cognition poorly loaded on this component (-0.24) and all other variables loaded heavily on this component ($>|0.8|$).

Omnibus testing of sleep disorders relationship to NMS of PD.

A hierarchical regression model with NMS_Total (which includes all 7 NMS outcome measures) as the dependent variable and dopaminergic therapy, age, and disease severity as independent variables was significant ($R^2=0.18$, $F_{3,82}=6.12$, $p=0.001$). In this model only age ($\beta=-0.26$, $p=0.012$) and dopaminergic therapy ($\beta=0.26$, $p=0.013$) were significant predictors of NMS_Total while disease severity was not ($\beta=0.19$, $p=0.06$). In summary, NMS_Total was correlated with age and dopaminergic therapy while controlling for disease severity, and these variables explained 18% of the variance in NMS_Total. Including the sleep disorders into this model significantly improved the model ($\Delta R^2=0.13$, $\Delta F_{3,79}=4.94$, $p=0.003$). The full model with NMS_Total as the dependent variable and age, disease severity, dopaminergic therapy, OSA, RBD, and RLS, as independent variables was significant ($R^2=0.31$, $F_{6,79}=5.97$, $p<0.001$) with age ($\beta=-0.25$, $p=0.011$), dopaminergic therapy ($\beta=0.24$, $p=0.013$), RBD ($\beta=0.26$, $p=0.008$), and RLS ($\beta=0.24$, $p=0.013$) as significant predictors of the NMS_Total. Disease severity ($\beta=0.18$, $p=0.064$) and OSA ($\beta=0.06$, $p=0.5$) were not significant predictors of NMS_Total. In summary, sleep disorders (specifically, RBD and

RLS) were significant contributors to NMS above and beyond that which is explained by age, dopaminergic therapy, and disease severity. Sleep disorders alone accounted for 13% of the variance in NMS_Total. Overall this model was significant and explained 31% of the variance in NMS_Total.

To insure that these results are not biased by including sleep-related symptoms into NMS_Total, an additional hierarchical regression model was conducted with NMS_NoSleep (which excludes sleep-related measures) as the dependent variable and age, disease severity and dopaminergic therapy as independent variables was significant ($R^2=0.19$, $F_{3,82}=6.23$, $p=0.001$). In this model age ($\beta=-0.22$, $p=0.031$), disease severity ($\beta=0.23$, $p=0.026$), and dopaminergic therapy ($\beta=0.27$, $p=0.01$) were significant predictors of NMS_NoSleep. In summary, NMS_NoSleep which omits sleep related symptoms was correlated with age, dopaminergic therapy, and disease severity. These variables explained 19% of the variance in NMS_NoSleep. Including the sleep disorders significantly improved the model ($\Delta R^2=0.11$, $\Delta F_{3,79}=4.02$, $p=0.01$). This full model with NMS_NoSleep as the dependent variable and age, disease severity, dopaminergic therapy, OSA, RBD, and RLS as independent variables was significant ($R^2=0.29$, $F_{6,79}=5.47$, $p<0.001$) with age ($\beta=-0.21$, $p=0.029$), disease severity ($\beta=0.22$, $p=0.025$), dopaminergic therapy ($\beta=0.25$, $p=0.011$), RBD ($\beta=0.22$, $p=0.022$), and RLS ($\beta=0.22$, $p=0.023$) as significant predictors of the NMS_NoSleep. Only OSA ($\beta=0.09$, $p=0.34$) was not a significant predictor in this model. In summary, sleep disorders (specifically, RBD and RLS) were significant

contributors to NMS_NoSleep above and beyond that which is explained by age, dopaminergic therapy, and disease severity. Sleep disorders alone accounted for 11% of the variance in NMS_NoSleep. Overall this model was significant and explained 29% of the variance in NMS_NoSleep.

Compared to no-RBD patients, yes-RBD patients scored significantly higher on NMS_Total ($t=-2.42, p=0.018$) as well as on NMS_NoSleep ($t=-2.45, p=0.016$). Similarly, compared to no-RBD, probable-RBD patients scored significantly higher on NMS_Total ($t=-2.71, p=0.008$) as well as on NMS_NoSleep ($t=-2.33, p=0.022$). There were no significant differences between probable-RBD and yes-RBD in either NMS_Total or 2. RLS patients showed similar patterns as yes-RLS patients, compared to no-RLS, scored significantly higher on NMS_Total ($t=-2.55, p=0.013$) as well as on NMS_NoSleep ($t=-2.39, p=0.019$) while controlling for age, disease severity, dopaminergic therapy, and the other sleep disorders (i.e., OSA and RBD). Finally, no differences were noted between yes-OSA and no-OSA patients on neither of the NMS Factors.

Multiple symptoms evaluation

A hierarchical regression model with the multiple symptoms evaluation (i.e., NMSQuest) as the dependent variable and age, disease severity, and dopaminergic therapy as independent variables was significant ($R^2=0.14, F_{3,82}=6.12, p=0.001$). In this model disease severity ($\beta=0.21, p=0.041$) and dopaminergic therapy ($\beta=0.22, p=0.036$) were significant predictor of the multiple symptoms evaluation while age ($\beta=-0.18, p=0.078$) was not. In summary, the

evaluation of multiple symptoms was correlated with dopaminergic therapy and disease severity while controlling for age and these variables explained 14% of the variance in the multiple symptoms evaluation. Including the sleep disorders did not improved the model ($\Delta R^2=0.042$, $\Delta F_{3,79}=1.35$, $p=0.27$). The full model with multiple symptoms evaluation as the dependent variable and age, disease severity, dopaminergic therapy, OSA, RBD, and RLS, as independent variables was not significant ($R^2=0.18$, $F_{6,79}=2.9$, $p=0.013$) and neither OSA ($\beta=0.007$, $p=0.95$), RBD ($\beta=0.17$, $p=0.11$), or RLS ($\beta=0.12$, $p=0.56$) were significant independent predators of the multiple symptoms evaluation. In summary, sleep disorders were not significant contributors to the multiple symptoms evaluation above and beyond that which is explained by age, dopaminergic therapy, and disease severity. Sleep disorders alone accounted for only 4% of the variance in this measure. Overall this model was not significant and explained only 18% of the variance in multiple symptoms evaluation.

Sleep

A hierarchical regression model with the subjective sleep evaluation (i.e., PDSS) as the dependent variable and age, disease severity, and dopaminergic therapy as independent variables was not significant ($R^2=0.13$, $F_{3,82}=4.14$, $p=0.009$). In this model only age ($\beta=0.24$, $p=0.02$) was a significant predictor of the subjective sleep evaluation while disease severity ($\beta=-0.2$, $p=0.06$) and dopaminergic therapy ($\beta=-0.16$, $p=0.13$) were not. In summary, modeling the evaluation of subjective sleep with dopaminergic therapy, disease severity, and age

was not significant at the pre-determined significance value ($p=0.007$), and these variables explained 13% of the variance in this measure. However, including the sleep disorders significantly improved the model ($\Delta R^2=0.13$, $\Delta F_{3,79}=4.59$, $p=0.005$). The full model with subjective sleep evaluation as the dependent variable and age, disease severity, dopaminergic therapy, OSA, RBD, and RLS, as independent variables was significant ($R^2=0.26$, $F_{6,79}=4.64$, $p<0.001$). Of the sleep disorders, only RBD ($\beta=-0.3$, $p=0.003$) was a significant predictor of the subjective sleep evaluation while OSA ($\beta=0.08$, $p=0.42$) and RLS ($\beta=-0.18$, $p=0.07$) were not. In summary, sleep disorders (specifically, RBD) were significant contributors to the subjective sleep evaluation above and beyond that which is explained by age, dopaminergic therapy, and disease severity. Sleep disorders alone accounted for 13% of the variance in this measure. Overall this model was significant and explained 29% of the variance in the subjective sleep evaluation.

As illustrated in Figure 2, post-hoc analyses revealed that compared to nRBD patients, yRBD scored significantly lower on the PDSS indicating poorer sleep for yRBD patients (yRBD=99.17±20.1 vs. nRBD =110.69±18.6, $t=-2.73$, $p=0.027$). Additionally, compared to nRBD, pRBD scored significantly lower on the PDSS (pRBD=93.67±21.1 vs. nRBD =110.69±18.6, $t=-3.02$, $p=0.003$). There were no significant differences between yRBD and pRBD ($t=1.05$, $p=0.3$). The PDSS includes two questions regarding motor control and dreaming that may be related to RBD diagnosis. Excluding these questions from the analysis did not significantly change the results.

Mood

A hierarchical regression model with mood evaluation (i.e., BDI-II) as the dependent variable and age, disease severity, and dopaminergic therapy as independent variables was not significant ($R^2=0.14$, $F_{3,75}=4.03$, $p=0.01$). In this model only age ($\beta=-0.28$, $p=0.01$) was a significant predictor of mood symptoms while disease severity ($\beta=0.1$, $p=0.36$) and dopaminergic therapy ($\beta=0.19$, $p=0.08$) were not. In summary, modeling the evaluation of mood with dopaminergic therapy, disease severity, and age was not significant at the pre-determined significance value ($p=0.007$), and these variables explained 14% of the variance in this measure. However, including the sleep disorders significantly improved the model ($\Delta R^2=0.1$, $\Delta F_{3,72}=3.2$, $p=0.028$) and the full model with mood evaluation as the dependent variable and age, disease severity, dopaminergic therapy, OSA, RBD, and RLS, as independent variables was significant ($R^2=0.24$, $F_{6,78}=3.79$, $p=0.002$). Of the sleep disorders, only RBD ($\beta=0.28$, $p=0.009$) was a significant predator of mood symptoms while OSA ($\beta=0.11$, $p=0.32$) and RLS ($\beta=0.99$, $p=0.33$) were not. In summary, sleep disorders (specifically, RBD) were significant contributors to the mood evaluation above and beyond that which is explained by age, dopaminergic therapy, and disease severity. Sleep disorders alone accounted for 10% of the variance in this measure. Overall this model was significant and explained 24% of the variance in the mood evaluation.

As illustrated in Figure 3, post-hoc analyses revealed that compared to nRBD patients, yRBD scored significantly higher on the BDI-II

(yRBD=10.56±6.58 vs. nRBD=6.54±5.17, $t=2.87$, $p=0.005$). Additionally, compared to nRBD, pRBD scored significantly higher on the BDI-II (pRBD=10.61±6.44 vs. nRBD=6.54±5.17, $t=2.5$, $p=0.014$). There were no significant differences between yRBD and pRBD ($t=0.09$, $p=0.93$). The BDI-II includes a question regarding changes in sleep and excluding this question from the analysis did not significantly change the results.

Quality of life

A hierarchical regression model with quality of life evaluation (i.e., PDQ-39) as the dependent variable and age, disease severity, and dopaminergic therapy as independent variables was significant ($R^2=0.22$, $F_{3,82}=8.94$, $p<0.001$). In this model, disease severity ($\beta=0.30$, $p=0.003$) and dopaminergic therapy ($\beta=0.28$, $p=0.006$) were significant predictors of quality of life while age ($\beta=-0.18$, $p=0.07$) was not. In summary, quality of life evaluation was correlated with dopaminergic therapy and disease severity while controlling for age, and these variables explained 22% of the variance in the quality of life evaluation. Including the sleep disorders significantly improved the model ($\Delta R^2=0.15$, $\Delta F_{3,79}=6.44$, $p=0.001$). The full model with PDQ-39 as the dependent variable and age, disease severity, dopaminergic therapy, OSA, RBD, and RLS, as independent variables was significant ($R^2=0.37$, $F_{6,79}=7.71$, $p<0.001$). Of the sleep disorders, only RLS ($\beta=0.33$, $p<0.001$) was a significant predictor of the quality of life while OSA ($\beta=0.12$, $p=0.19$) and RBD ($\beta=0.18$, $p=0.05$) were not. In summary, sleep disorders (specifically, RLS) were significant contributors to the quality of life evaluation

above and beyond that which is explained by age, dopaminergic therapy, and disease severity. Sleep disorders alone accounted for 15% of the variance in this measure. Overall this model was significant and explained 37% of the variance in the quality of life evaluation.

As illustrated in Figure 4, post-hoc analyses revealed that compared to no-RLS patients, yes-RLS patients scored significantly higher on the PDQ-39 (yes-RLS=48.68±17.76 vs. no-RLS=30.76±19.43, $t=-3.61$, $p=0.001$) indicating poorer quality of life for these patients.

Cognition

A hierarchical regression model with cognition evaluation (i.e., MoCA) as the dependent variable and age, disease severity, and dopaminergic therapy as independent variables was not significant ($R^2=0.12$, $F_{3,82}=3.54$, $p=0.018$). In this model only age ($\beta=-0.31$, $p=0.004$) was a significant predictor of cognitive performance while dopaminergic therapy ($\beta=-0.15$, $p=0.14$) and disease severity ($\beta=-0.03$, $p=0.77$) were not. In summary, modeling the cognitive evaluation with dopaminergic therapy, disease severity, and age was not significant at the pre-determined significance value ($p=0.007$), and these variables explained 12% of the variance in this measure. Including the sleep disorders did not significantly improved the model ($\Delta R^2=0.05$, $\Delta F_{3,79}=4.94$, $p=0.176$). The full model with MoCA as the dependent variable and age, disease severity, dopaminergic therapy, OSA, RBD, and RLS, as independent variables was not significant ($R^2=0.17$, $F_{6,79}=2.66$, $p=0.02$). Neither OSA ($\beta=-0.17$, $p=0.12$), RBD ($\beta=-0.13$, $p=0.2$), or

RLS ($\beta=-0.08, p=0.42$) were significant predators of the cognitive performance. In summary, sleep disorders were not significant contributors to the cognitive evaluation above and beyond that which is explained by age, dopaminergic therapy, and disease severity. Sleep disorders alone accounted for only 5% of the variance in this measure. Overall this model was not significant and explained 17% of the variance in the cognitive evaluation.

Fatigue

A hierarchical regression model with fatigue evaluation (i.e., MFSI-SF) as the dependent variable and age, disease severity, and dopaminergic therapy as independent variables was not significant ($R^2=0.11, F_{3,82}=3.47, p=0.02$). In this model only dopaminergic therapy ($\beta=0.26, p=0.015$) was a significant predictor of fatigue while age ($\beta=-0.19, p=0.07$) and disease severity ($\beta=0.02, p=0.82$) were not. In summary, modeling the fatigue evaluation with dopaminergic therapy, disease severity, and age was not significant at the pre-determined significance value ($p=0.007$), and these variables explained 11% of the variance in this measure. However, including the sleep disorders significantly improved the model ($\Delta R^2=0.13, \Delta F_{3,79}=4.3, p=0.007$). The full model with MFSI-SF as the dependent variable and age, disease severity, dopaminergic therapy, OSA, RBD, and RLS, as independent variables was significant ($R^2=0.27, F_{6,79}=4.1, p=0.001$). Of the sleep disorders, RBD ($\beta=0.26, p=0.01$) and RLS ($\beta=0.23, p=0.02$) were significant predators of fatigue while OSA ($\beta=0.05, p=0.62$) was not. In summary, sleep disorders (specifically, RLS and RBD) were significant contributors to the fatigue

evaluation above and beyond that which is explained by age, dopaminergic therapy, and disease severity. Sleep disorders alone accounted for 13% of the variance in this measure. Overall this model was significant and explained 27% of the variance in the fatigue evaluation.

As illustrated in Figure 5, post-hoc analyses revealed that compared to no-RBD patients, yes-RBD scored significantly higher on the MFSI-SF (yes-RBD=12.06±13.3 vs. no-RBD=6.0±7.7, $t=2.26$, $p=0.028$). Additionally, compared to no-RBD, probable-RBD scored significantly higher on the MFSI-SF (probable-RBD=16.0±16.27 vs. no-RBD=6.0±7.7, $t=2.69$, $p=0.011$). There were no significant differences between yes-RBD and probable-RBD ($t=-0.97$, $p=0.336$). Assessing the MFSI-SF subscales revealed that there were significant differences between the RBD groups on the Physical ($F=4.48$, $p=0.014$) and Emotional ($F=6.74$, $p=0.002$) subscales. More specifically, compared to no-RBD, probable-RBD scored significantly higher on the Physical subscale (probable-RBD=7.79±5.2 vs. no-RBD=4.08±3.92, $t=2.98$, $p=0.004$) and the Emotional subscale (probable-RBD=6.75±4.95 vs. no-RBD=2.77±2.66, $t=3.5$, $p=0.001$). Additionally, compared to the yes-RBD group, probable-RBD scored higher on the Emotional subscale (probable-RBD=6.75±4.95 vs. yes-RBD=4.22±3.8, $t=-2.12$, $p=0.04$).

As illustrated in Figure 6 Post-hoc analyses revealed that compared to no-RLS patients, yes-RLS patients scored significantly higher on the fatigue scale (yes-RLS=17.26±14.3 vs. no-RLS=9.55±12.5, $t=-2.29$, $p=0.024$) indicating

increased fatigue for these patients. Assessing the MFSI-SF subscales revealed that compared to no-RLS, yes-RLS patients scored significantly higher on the Physical (yes-RLS=7.58±4.5 vs. no-RLS=5.22±4.5, $t=-2.01$, $p=0.047$) and Mental subscales (yes-RLS=8.63±5.12 vs. no-RLS=4.9±3.77, $t=-3.51$, $p=0.001$).

Subjective daytime sleepiness

A hierarchical regression model with subjective daytime sleepiness evaluation (i.e., ESS) as the dependent variable and age, disease severity, and dopaminergic therapy as independent variables was not significant ($R^2=0.09$, $F_{3,82}=2.61$, $p=0.057$). In this model only age ($\beta=-0.29$, $p=0.008$) was a significant predictor of subjective daytime sleepiness while dopaminergic therapy ($\beta=0.05$, $p=0.81$) and disease severity ($\beta=0.05$, $p=0.65$) were not significant predictors of subjective daytime sleepiness. In summary, modeling the subjective daytime sleepiness evaluation with dopaminergic therapy, disease severity, and age was not significant at the pre-determined significance value ($p=0.007$), and these variables explained 9% of the variance in this measure. Including the sleep disorders did not improved the model ($\Delta R^2=0.02$, $\Delta F_{3,79}=0.65$, $p=0.59$). The full model with subjective daytime sleepiness as the dependent variable and age, disease severity, dopaminergic therapy, OSA, RBD, and RLS, as independent variables was not significant ($R^2=0.11$, $F_{6,79}=1.61$, $p=0.15$) and either OSA ($\beta=0.1$, $p=0.34$), RBD ($\beta=0.01$, $p=0.93$), or RLS ($\beta=0.11$, $p=0.29$) were significant predators of subjective daytime sleepiness. In summary, sleep disorders were not significant contributors to the subjective daytime sleepiness evaluation above and beyond that which is

explained by age, dopaminergic therapy, and disease severity. Sleep disorders alone accounted for only 2% of the variance in this measure. Overall this model was not significant and explained only 11% of the variance in the subjective daytime sleepiness evaluation.

Aim 2 Results: Sleep Disorders, Dopaminergic Therapy, and Objective Daytime Sleepiness

There was a significant negative correlation ($r=-0.3, p=0.005$) between subjective (ESS) and objective (MSLT-SOL) measures of daytime sleepiness such that those reporting more daytime sleepiness on the ESS had shorter mean sleep onset during the MSLT. Additionally, there was a significant negative correlation ($r=-0.27, p=0.013$) between dopamine agonist equivalents dosage and MSLT-SOL such that those taking higher dosages of dopamine agonist had shorter mean sleep onset during the MSLT. In summary, taking higher dosages of dopamine agonists was associated with more objective sleepiness prior to controlling for relevant variables (i.e., age and disease severity). There were no significant relationships between sleepiness measures (ESS and MSLT-SOL) and levodopa-only equivalents dosage or total dopaminergic therapy.

A hierarchical regression model with objective daytime sleepiness (i.e., MSLT-SOL) as the dependent variable and age, disease severity, and dopaminergic therapy as independent variables was not significant ($R^2=0.04, F_{3,82}=0.98, p=0.41$). In this model neither age ($\beta=0.22, p=0.84$), dopaminergic therapy ($\beta=-0.18, p=0.11$) nor disease severity ($\beta=0.06, p=0.6$) were significant

predictors of objective daytime sleepiness. In summary, modeling the objective daytime sleepiness evaluation with dopaminergic therapy, disease severity, and age was not significant at the pre-determined significance value ($p=0.007$), and these variables explained only 4% of the variance in this measure. Including the sleep disorders did not improved the model ($\Delta R^2=0.073$, $\Delta F_{3,79}=2.59$, $p=0.1$). The full model with objective daytime sleepiness as the dependent variable and age, disease severity, dopaminergic therapy, OSA, RBD, and RLS, as independent variables was not significant ($R^2=0.11$, $F_{6,79}=1.58$, $p=0.16$) and either OSA ($\beta=-0.2$, $p=0.07$), RBD ($\beta=-0.04$, $p=0.7$), or RLS ($\beta=-0.19$, $p=0.08$) were significant predators of the objective daytime sleepiness. In summary, sleep disorders were not significant contributors to the objective daytime sleepiness evaluation above and beyond that which is explained by age, dopaminergic therapy, and disease severity. Sleep disorders alone accounted for only 7% of the variance in this measure. Overall this model was not significant and explained only 11% of the variance in the objective daytime sleepiness evaluation.

Similar and non-significant results were obtained when including the separate variables dopamine agonist-only and carbadopa/levodopa-only equivalence dosages. In summary, while there was a significant relationship between MSLT-SOL and dopamine agonist-only, this relationship was not significant when controlling for age and disease severity, and sleep disorders did not improve this model.

Parts of this dissertation has been modified for publication and submitted.

Written consent was provided by coauthors. The dissertation author was the primary author on these paper and will be cited as: Neikrug AB, Maglione JE, Liu L, Natajaran L, Avanzino JA, Corey-Bloom J, Palmer B, Lored JS, and Ancoli-Israel S. Effects of sleep disorders on the non-motor symptoms of Parkinson disease.

DISCUSSION

This study assessed the relationship between sleep disorders and multiple NMS in PD. Using dimension reduction techniques to derive a single factor score for each individual representing overall NMS, the analyses revealed that sleep disorders are independent and significant contributors to the non-motor impairment experienced in PD. Specifically, the data revealed that having OSA, RBD, and/or RLS predict more NMS impairment (i.e., higher scores on the NMS factor) with a moderate effect size ($R^2=0.31$) after controlling for age, disease severity, and dopaminergic therapy. The relationship between sleep disorders and overall NMS held true when omitting the sleep measures from the derived factor which indicates that sleep symptoms per-se did not bias the finding that having sleep disorders increase overall NMS endorsement by PD patients. The multivariate results revealed that sleep disorders are significant predictors of increased subjective reports of nighttime sleep disturbances, poor mood, lower quality of life, and increased fatigue.

This study assessed for OSA, RBD, RLS, and PLMS. However, as only 2 patients met criteria for PLMS this disorder was removed from the analyses. Periodic leg kicks were reported to be more frequent in diseases showing an impaired dopaminergic transmission, like PD, as opposed to disorders lacking this condition, such as Alzheimer's disease (Bliwise et al., 1998) and multisystem atrophy (Wetter et al., 2000). In addition, Happe and colleagues (Happe et al., 2003) observed an association between numbers of periodic leg kicks and

dopaminergic cells loss examined with advanced imaging techniques in PD patients. Previous study in our laboratory concurred with these reports and showed high prevalence in periodic kicks during the night in PD (Covassin et al., 2012). However, these studies, in general, assessed overall periodic leg kicks. Periodic leg kicks are considered a sleep disorder (i.e., PLMS) only when these events are associated with arousals that are independent of arousals caused by apnea events. One possibility for the low incidents of PLMS in this sample is that in this study, leg kicks associated with arousals were scored only when these were not adjacent to arousals cause by apnic events and therefore and due to the high prevalence of OSA in this sample PLMS scoring may have been under estimated. Future studies should assess PLMS prevalence in PD only after treatment of OSA.

Of the sleep disorders included in the analyses, RBD and RLS were significant predictors of the NMS Factor score but OSA was not. More specifically, these results showed that PD patients with RBD and/or with RLS experience and have higher NMS Factor scores than PD patients without these disorders after controlling for age, disease severity, dopaminergic therapy and presence of OSA. Additionally, these results showed that PD patients with RBD reported increased symptoms of depression, fatigue, nighttime sleep dysfunction, and quality of life. PD patients with RLS reported more symptoms of fatigue and poorer quality of life. Since the omnibus testing revealed that RBD and RLS were significant predictors of increase NMS in PD, these disorders were further analyzed.

RBD and NMS in PD

Most previous studies of RBD in PD suggested that PD patients with RBD exhibit unique clinical characteristics. However, conflicting findings have been reported. For example, RBD in PD has been associated with male gender (Gjerstad et al., 2008; Scaglione et al., 2005), disease severity (Sixel-Doring et al., 2011) longer disease duration (De Cock et al., 2007; Scaglione et al., 2005; De Cock et al., 2007), increased dopaminergic therapy (Wetter, Trenkwalder, Gershanik, & Hogl, 2001; Gjerstad et al., 2008), poorer cognitive performance (Vendette et al., 2007) increase falls (Postuma et al., 2008b), and autonomic dysfunction (Postuma et al., 2008a). However, other studies did not observe associations with male gender (Sixel-Doring et al., 2011; De Cock et al., 2007), disease severity (Sinforiani et al., 2006), disease duration (Postuma et al., 2008a; Sinforiani et al., 2006), and dopaminergic therapy (Postuma et al., 2008b; Scaglione et al., 2005; Sinforiani et al., 2006; De Cock et al., 2007). There are many possible reasons for such conflicting reports. Most important are the methodological differences in diagnosing RBD. Diagnosis of RBD is challenging and includes subjective and objective assessments which are costly and time consuming (Neikrug & Ancoli-Israel, 2012). Several of these studies (Gjerstad et al., 2008; Scaglione et al., 2005; De Cock et al., 2007; Sinforiani et al., 2006) employed only clinical/subjective assessment of RBD which has shown to have very poor diagnostic accuracy in PD patients (Eisensehr, Lindeiner, Jager, & Noachtar, 2001). Additionally, in many of these studies NMS domains were assessed with a single question and most studies

assessed a single NMS domain post-hoc. In this study, increase NMS was tested across multiple domains. Additionally, this study utilized established measures to assess a given domain and did not utilize single questions for indication of a specific NMS. The results of this study show that having RBD is associated with more reports of sleep dysfunction, depressive symptoms, fatigue, and overall quality of life.

While increasing reports suggest that PD patients with versus without RBD are clinically different, the etiology of such differences is not well understood. According to Braak et al.'s (Braak, Ghebremedhin, Rub, Bratzke, & Del Tredici, 2004) six-stage neuropathological model of PD, the first stages of the disease are marked by pathology at the dorsal motor nucleus of the vagal nerve and olfactory pathology at the olfactory bulb and anterior olfactory nucleus. The pathology during stage I and II is confined to olfactory sites, medulla oblongata, and pontine tegmentum. In stage III pathology extends into basal portions of the midbrain and forebrain including the amygdala and forebrain. During this stage pathology encroaches the substantia nigra which leads to the classic clinical manifestation of PD. While some of the NMS of PD are explained by this process, further research is necessary to assess the different pathology between PD patients with versus without RBD and rather those with RBD represent a subtype of PD with different disease progression and phenomenological presentation.

RBD and sleep.

There are only few studies that used objective criteria for RBD in PD and also assessed for sleep-related differences. Previous studies have shown that PSG-recorded measures (total sleep time, sleep efficiency, sleep architecture) do not greatly differ between PD patients with versus without RBD (De Cock et al., 2007; Postuma et al., 2008b; Wetter et al., 2001). Nonetheless, a study using actigraphy to evaluate nighttime disturbances reported that those with subjectively diagnosed RBD had more wake bouts during the night than those without RBD (Naismith, Rogers, MacKenzie, Hickie, & Lewis, 2010). It is important to point out that some studies questioned the ability of PD patients with RBD to recall the experienced nighttime disturbances (Iranzo et al., 2005; Happe et al., 2005). More research using objective assessment of RBD and assessment of subjective sleep complaints are necessary to better understand these results. Nonetheless, in the current study, RBD patients clearly reported more subjective sleep dysfunction even when omitting questions that may be related to RBD diagnosis.

RBD and mood.

In the elderly, sleep disturbances are a risk factor for depression onset and relapse (Geerlings, Beekman, Deeg, Twisk, & Tilburg, 2002). In PD, symptoms of depression have been shown to be associated with subjectively assessed sleep disturbances (Happe et al., 2001; Naismith, Hickie, & Lewis, 2010; Menza & Rosen, 1995). To my knowledge, this is the first study to show an association between an objectively assessed RBD and symptoms of depression in PD. These

findings indicate that PD patients with confirmed RBD (yes-RBD) and those with suspected RBD (probable-RBD) experience more depressive symptoms compared to those with no evidence of RBD (no-RBD). Interestingly, antidepressant medications were also used more frequently in the yes-RBD and probable-RBD groups compared to the no-RBD group (Table 4b). This contrasts with the results of prior studies in patients with idiopathic RBD (Postuma & Montplaisir, 2006), and studies of RBD in PD (Postuma et al., 2008a; De Cock et al., 2007; Gjerstad et al., 2008). However, in the study by Gjerstad et al. (Gjerstad et al., 2008), RBD was diagnosed based on a sleep questionnaire not validated for RBD diagnosis. In the study by Postuma et al. (Postuma et al., 2008a), depression was assessed using the UPDRS Part 1 which includes only a single question on depression. In the current study, the groups differed on the BDI-II as well as in Part 1 of the UPDRS (Table 4b). While the study by Postuma et al. (Postuma et al., 2008a) did not report a relationship with depression per se, they noted that PD patients with RBD scored significantly lower on the “role limitations – emotional” subscale and on the mental health summary score of the Short Form-36, a well validated quality of life measure (Ware & Sherbourne, 1992; McHorney, Ware Jr, & Raczek, 1993). The study by De Cock et al. (De Cock et al., 2007) assessed for symptoms of depression using the BDI-II, however they only compared the number of patients that exceeded a score of 13 (an arbitrary cut-off score) and they did not compare or provide average BDI-II scores. Studies assessing depression in PD suggest that depression primarily results of brain dysfunction rather than situational factors

(Tandberg et al., 1997). In fact, presence of RBD may indicate more progressive neuropathological processes which may explain such findings. As this study assessed for NMS, it appropriately included an assessment of depressive symptoms rather than a diagnosis of depression. Future research using clinical criteria for diagnosis of depression would be appropriate to further explore this possible relationship.

RBD and fatigue.

To my knowledge, this is the first study to assess an association between RBD and fatigue in PD. The findings suggest that PD patients with RBD and those with suspected RBD experience more fatigue compared to those with no RBD. When assessing the subscales, probable-RBD group showed increase emotional and physical fatigue over those in the no-RBD group. Interestingly, probable-RBD showed increased emotional fatigue compared to yes-RBD patient. While yes-RBD group scored higher on the overall scale, they were not different from the no-RBD group on individual subscales. Subscale differences should be considered with caution as these were post-hoc and exploratory in nature. Nonetheless, the overall increase in fatigue appears to be a robust finding with moderate effect size ($R^2=0.27$). Increased fatigue may be a function of worse sleep as is suggested by the higher subjective reports of nighttime sleep disturbances in this sample of PD patients with RBD. Nonetheless, additional studies are necessary to explore this association.

RBD and quality of life.

In general sleep dysfunction has been shown to be associated with low quality of life in PD patients (Happe & Berger, 2001). This is also seen in these analyses as there was a strong negative association ($r=-0.69$, $p<0.001$) between the subjective sleep dysfunction (PDSS) and quality of life (PDQ-39) such that those reporting more sleep dysfunction also reported lower quality of life. This is similar to previous findings (Scaravilli, Gasparoli, Rinaldi, Polesello, & Bracco, 2003) and further support the assertion that sleep disturbances negatively impact quality of life. In this study, sleep disorders were significant predictors of poor quality of life. In the model tests, RBD was not quite significant ($p=0.051$) but the overall model had a relatively strong effect size ($R^2=0.37$). Partialing the unique effect of RBD in this model revealed a moderate effect size (partial $R^2=0.22$). Additionally, there was a significant and moderate relationship between the subjective assessment of RBD (RBDSQ) and quality of life (PDQ-39) ($r=0.26$, $p=0.01$) such that increase reporting of RBD symptoms was associated with poorer quality of life. A study by Postuma et al (Postuma et al., 2008a) did not observe a significant difference between PD patients with versus without RBD on the PDQ-39. However, this study reported that RBD patients demonstrated lower quality of life scored on a different quality of life measure (Short-Form-36). It is important to point out that the term 'quality of life' is used here only to represent the performance on the specific measure. However, there is no doubt that all the symptoms assessed in this study contribute and are related to the overall quality of

life that these patients experience. Therefore, even though RBD did not reach the ‘significance’ level in predicting the performance on the quality of life measure, the relationship observed to the other NMS characterize RBD patients as having poorer quality of life.

RBD and cognition.

This study did not find a relationship between RBD and cognitive performance in this PD sample which is similar to a previous study that utilized a single measure of cognitive impairment (Sixel-Doring et al., 2011). However, multiple studies have shown that PD patients with RBD tend to demonstrate more cognitive impairment (Gagnon et al., 2006; Marion, Qurashi, Marshall, & Foster, 2008; Sinforiani et al., 2006; Sinforiani et al., 2008; Vendette et al., 2007). There are some fundamental differences that prevent concluding that these results are contradicting to previous studies. First, some of these studies used only the subjective criteria for RBD diagnosis (Marion et al., 2008; Sinforiani et al., 2006; Sinforiani et al., 2008) and had smaller sample size (Vendette et al., 2007; Marion et al., 2008). Also, disease severity in these studies tended to be higher than that included in our study (Marion et al., 2008). Finally, we used only a single measure of cognitive performance while other studies used a comprehensive neurocognitive assessment (Sinforiani et al., 2006; Sinforiani et al., 2008; Vendette et al., 2007) and therefore their findings better represent overall cognitive functioning.

RLS and NMS in PD

Our results suggest that compared to PD patients with no RLS, PD patients with RLS experience overall more NMS and specifically more symptoms of fatigue and poorer quality of life. Only few studies have systematically assessed clinical differences between PD patients with versus without RLS. Studies reporting on clinical differences in these populations revealed mixed results. For example, a study by Krishnan et al. (Krishnan, Bhatia, & Behari, 2003) of 126 PD patients from India reported male predominance in those with RLS, while a study by Verbaan et al. (Verbaan, van Rooden, van Hilten, & Rijsman, 2010) of 269 PD patients from the Netherlands reported higher female predominance. These same studies reported conflicting findings regarding presence of depression in PD patients with RLS. While the study by Krishnan et al. suggested that PD patients with RLS have higher rates of depression, the study by Verbaan et al. did not find such differences. Nonetheless, Verbaan et al. reported significant correlation between the severity of the RLS and symptoms of depression. Depression was assessed differently in these studies. Krishnan et al. assessed for depression according to the DSM-IV criteria and Verbaan et al. used the BDI-II. Our results reflect similar findings to those reported by Verbaan et al. and did not observe differences in depression symptom reporting on the BDI-II between PD patients with versus without RLS. It is important to point out that the different populations utilized in these studies reviewed above may prevent appropriate comparisons. Additionally, in Krishnan et al., the prevalence of RLS was only 7.9% (n=10),

significantly lower than expected (Oerlemans & de Weerd, 2002; Ondo et al., 2002; Braga-Neto et al., 2004) and no error protection were utilized for the multiple comparisons in their study.

Several studies found differences in subjectively reported sleep-related disturbances and sleepiness between PD patients with versus without RLS (Nomura, Inoue, Miyake, Yasui, & Nakashima, 2005; Krishnan et al., 2003; Loo & Tan, 2008). The study by Verbaan et al. (Verbaan et al., 2010) also reported that severity of RLS in PD patients was correlated with more NMS including, poorer cognitive performance, increased daytime sleepiness, more psychotic symptoms, more depressive symptoms, and increased nocturnal sleep complaints. However, neither of these studies controlled for age, disease severity, dopaminergic therapy, and presence of other sleep disorders. In our analyses, when controlling for these variables, RLS was not a significant predictor of subjective reports of sleep dysfunction. Nonetheless, our results would have suggested a significant difference between the groups if no adjustments were used.

To my knowledge, this is the first study to show an association between RLS and fatigue, and RLS and quality of life in a PD sample. These findings suggest that PD patients with RLS experience more fatigue and poorer quality of life compared to those with no RLS. Further studies assessing this relationship are necessary to establish the relevance of these findings.

Sleep Disorders, Dopaminergic Therapy, and Daytime Sleepiness

These results of this study suggest that sleep disorders do not significantly explain daytime sleepiness in PD, measured either subjectively or objectively. In previous studies assessing sleepiness using MSLT in an unselected sample of PD patients, average overall MSLT-SOL was 11 minutes which is similar to the current findings (overall MSLT-SOL=10.97±4.8) (Razmy, Lang, & Shapiro, 2004; Arnulf et al., 2000). However, while in their study pathological sleepiness (MSLT-SOL≤5min) was reported in 18% of PD patients (Razmy et al., 2004), in this study only 10.5% (n=9) of the sample exhibited pathological sleepiness. Previous studies have suggested a relationship between nighttime sleep onset latency, total sleep time at night, and objective measures of daytime sleepiness such that those falling asleep faster at night and have longer nighttime sleep duration tend to be sleepier during the day, however there are no data to suggest an association between objectively assessed nighttime disturbance and daytime sleepiness (Arnulf, 2005). This is the first study to systematically assess daytime sleepiness in PD with RBD and RLS. Nonetheless, previous studies that assessed sleepiness in PD with OSA did not find a relationship between OSA measures and daytime sleepiness which align with the findings here (Cochen De Cock et al., 2010; Arnulf et al., 2002). As noted earlier, there are conflicting reports regarding the relationship between dopaminergic treatments and excessive daytime sleepiness in PD. The results of this study align with these confusing findings. While there was a significant association between daytime sleepiness and dopamine agonists, this was no longer

significant after controlling for age and disease severity. Additionally, there was no relationship between daytime sleepiness and the overall daily dopaminergic therapy dosages. A study by Arnulf et al. (Arnulf et al., 2002) found no correlation between the MSLT results and the daily dose of either dopamine agonists or daily levodopa equivalents. However, they observed a weak positive relationship between the MSLT and daily dose of levodopa.

Nonetheless, it is important to point out that these results suggested a relationship between subjectively reported sleep dysfunction during the night (PDSS) and subjective daytime sleepiness (ESS) which is similar to previous reports in PD (Naismith et al., 2010). Additionally, this study showed a weak, yet significant relationship between the subjective daytime sleepiness (ESS) and the MSLT-SOL, similar to results previously reported in the PD population (Arnulf et al., 2002). Taken together, research has demonstrated the complexity of daytime sleepiness in PD which is likely, as suggested previously, a multifactorial phenomenon and cannot be easily modeled.

Strengths and Limitations

The major strengths of this study include the systematic and objective assessment of sleep disorders in this sample of PD patients. Nonetheless, we did not have sufficient data to include the diagnosis of insomnia into this study. Insomnia may also involve worse non-motor outcomes and future studies will need to assess the impact of insomnia on non-motor symptoms impairment. The availability of overnight PSG data allowed for reliably diagnosing OSA, RBD, and

PLMS in PD. This study used subjective and objective measures daytime sleepiness which allowed for a systematic assessment. Additionally, this study utilized multiple previously-validated measures of NMS and the employed advanced statistics to assess different NMS in a cohesive manner and avoiding multiple comparisons. Nonetheless, this study had several limitations. Video recordings during PSG were available for less than half of the sample for diagnosing RBD. However, detailed clinical notes were maintained by the technician and these notes were available for all patients. Additionally, the scorer of EMG-activity was not blind to technician's notes as notes were made on the PSG records. In our study only one-night PSG recording was conducted and while this more closely resembles clinical findings, single night recordings may miss RBD occurrences due to high night-to-night variability (Sixel-Doring, Schweitzer, Mollenhauer, & Trenkwalder, 2011). However, while we may have underestimated RBD in our sample, our RBD occurrence rate is similar to other studies using similar methodology (Sixel-Doring et al., 2011; Eisensehr et al., 2001). Our study was also limited to a subjective assessment of self-reported symptoms and future studies should include objective measures and/or clinical interviews to further support such findings. We also did not include motor impairment or pain into the models, which may bias and attenuate findings as it is hypothesized that these variables also have a major impact on overall non-motor impairment and quality of life. Future studies may include these variables to assess the impact of motor functioning and pain on the non-motor impairment score. Also, due to

inclusion/exclusion criteria our sample may not be generalizable to the overall PD population. Finally, as we used multiple measures of NMS we did not have sufficient power to strictly protect error-rate of post-hoc analyses. However, these were exploratory in nature and should be used with caution. While we used advanced statistical methods that allowed us to conduct omnibus testing of the relationship between the sleep disorders and the multiple NMS of PD, our sample size was somewhat small for running PCA.

Parts of this dissertation has been modified for publication and submitted. Written consent was provided by coauthors. The dissertation author was the primary author on these paper and will be cited as: Neikrug AB, Maglione JE, Liu L, Natajara L, Avanzino JA, Corey-Bloom J, Palmer B, Lored JS, and Ancoli-Israel S. Effects of sleep disorders on the non-motor symptoms of Parkinson disease.

CONCLUSION

In summary, this study showed that in the PD patient population, the presence of co-morbid sleep disorders predicts more NMS symptoms in general. More specifically, having sleep disorders predicted increased reports of nighttime sleep dysfunction, poor mood, lower quality of life, and increased fatigue. Of the sleep disorders assessed in this study, RBD and RLS were indicators of increased NMS but OSA was not. The findings of increased NMS in RBD adds further support to a growing body of literature that suggests that RBD is related to increase frequency and severity of non-motor impairment and subsequent poorer quality of life, and further supports the hypothesis that RBD may be an indicator of a subtype of PD patients with a differing clinical presentation and pathophysiological processes. This is the first study to systematically assess the effect of RLS on NMS in PD and further research is needed to corroborate these findings.

The sleep disturbances seen in PD are multifactorial and likely result from a combination of neurodegenerative and neurochemical processes and changes that occur in brain centers responsible for sleep regulatory such as the thalamus, midbrain, and forebrain (Lees et al., 1988; Askenasy, 2001; Rye & Jankovic, 2002). The impact of sleep disorders on quality of life is well established and previous studies in older adults demonstrated that sleep dysfunction is a key factor for institutionalization of older adults and increase caregiver burden (Pollak & Perlick, 1991).

This study also assessed possible relationships to daytime sleepiness in this population. The models tested here were not significant and suggested that daytime sleepiness is not significantly associated with sleep disorders, age, disease severity, and dopaminergic therapy. While previous studies and this study noted simple correlations between daytime sleepiness, sleep, and dopaminergic treatment, such findings appear to result from not appropriately controlling for other important variables such as disease severity and age. Therefore, these results align with previous research in that it demonstrates the multifactorial nature of daytime sleepiness in PD. Further research is needed to better understand this devastating phenomenon and to direct intervention approach.

These findings that sleep disorders are unique predictors of increase NMS and poorer quality of life is important for considering disease management approaches. Additional studies are now required to determine whether the treatment of sleep disorders in PD may offer significant benefit in terms of overall NMS and quality of life. A recent pilot study that provided behavioral treatment for sleep in a small sample of PD patients suggested that improving nighttime sleep in these patients improves quality of life for the patients and their caregivers (Leroi, Baker, Kehoe, Daniel, & Byrne, 2010). While treating sleep disorders will likely not affect PD progression, it has the potential for improving NMS and by that potentially improve the lives of the patients and their caregivers.

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FIGURES

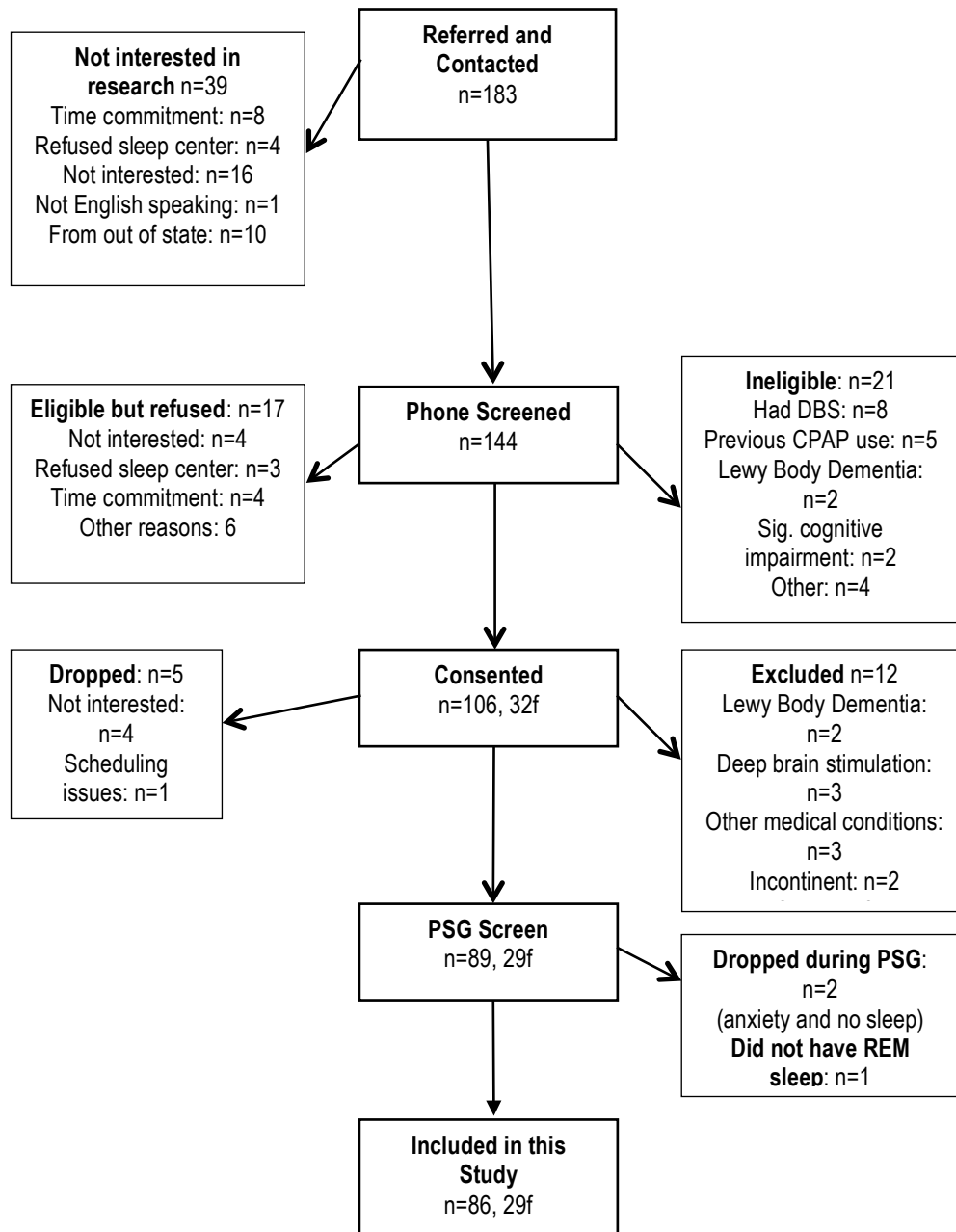


Figure 1: Consort Table

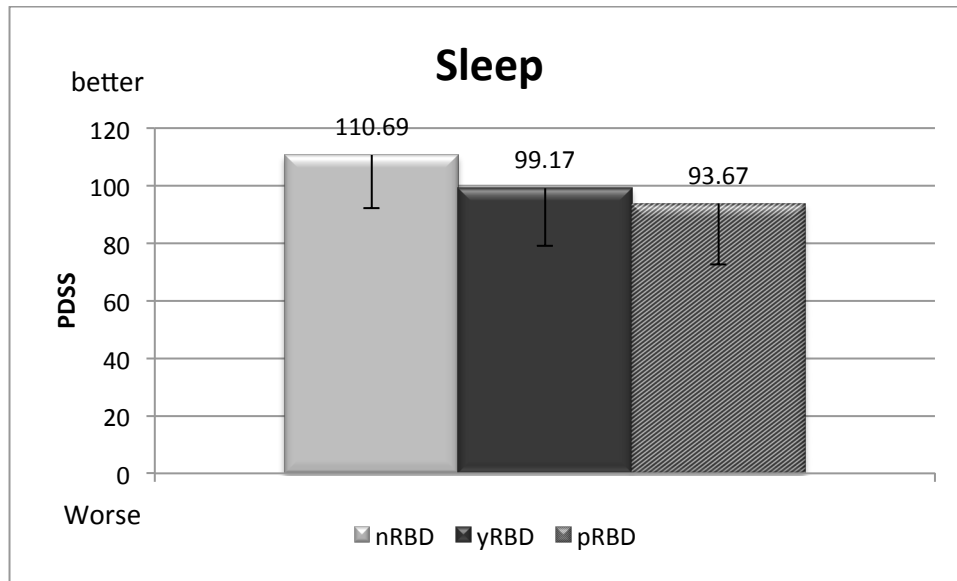


Figure 2: RBD and Subjective Sleep Complaints

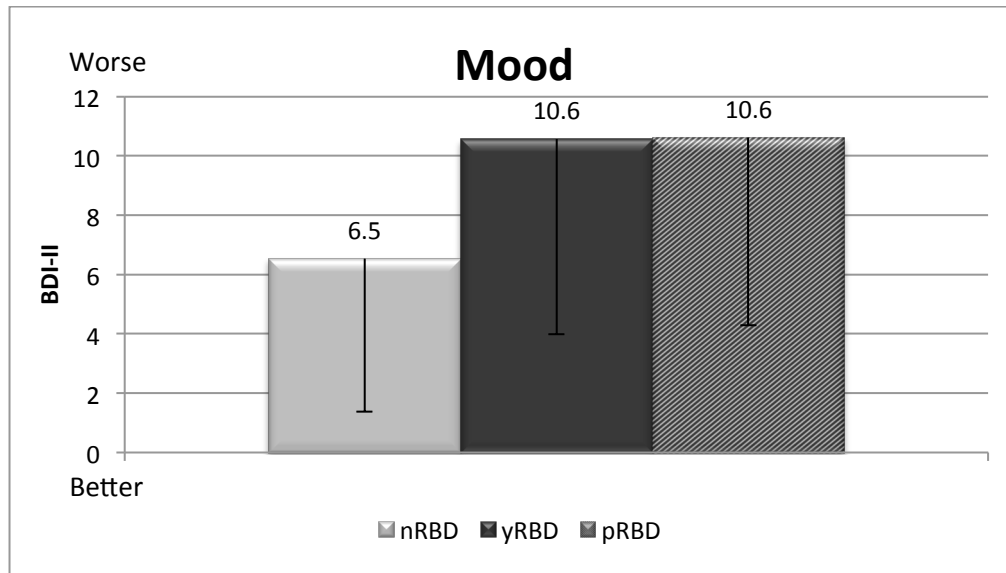


Figure 3: RBD and Mood

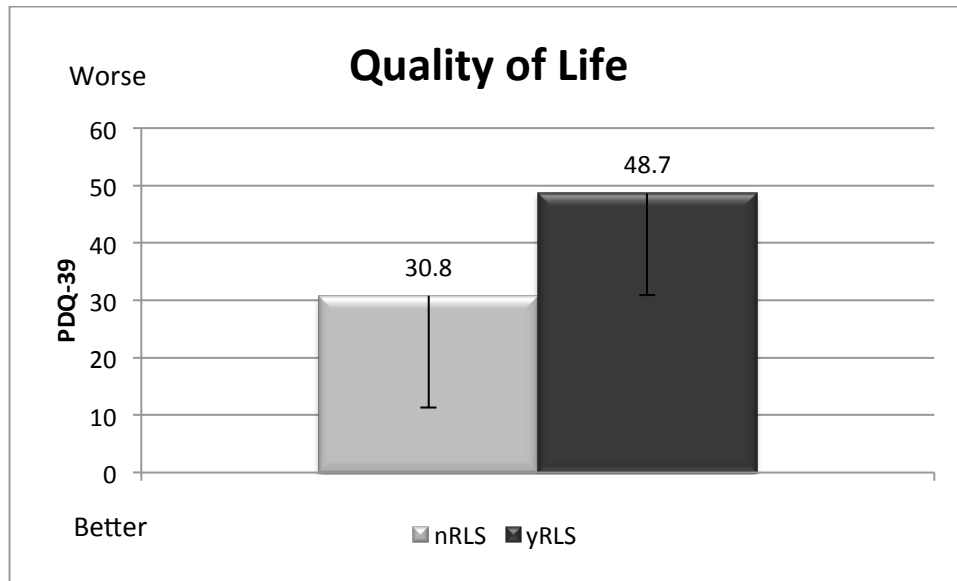


Figure 4: RLS and Quality of Life

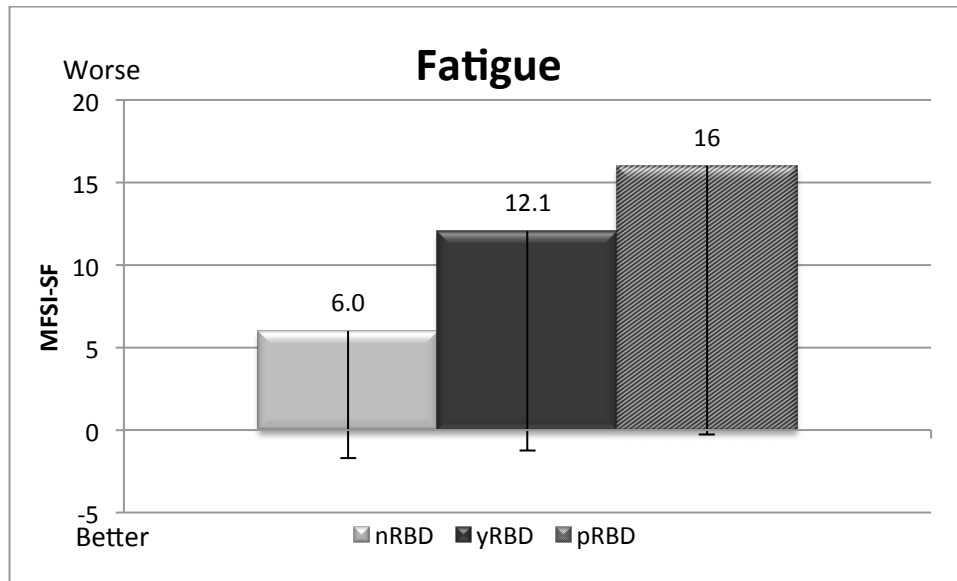


Figure 5: RBD and Fatigue

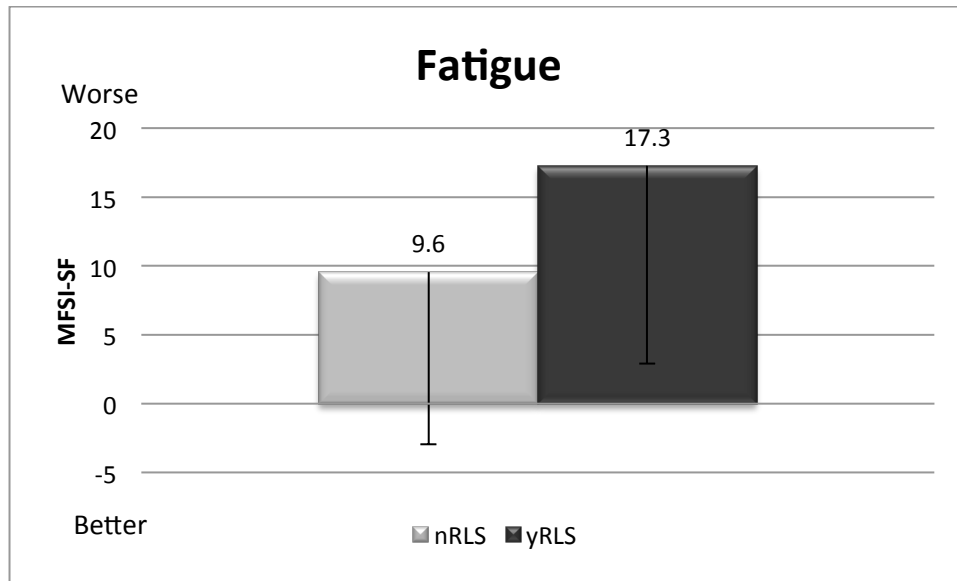


Figure 6: RLS and Fatigue

Parts of this dissertation has been modified for publication and submitted.

Written consent was provided by coauthors. The dissertation author was the primary author on these paper and will be cited as: Neikrug AB, Maglione JE, Liu L, Natajaran L, Avanzino JA, Corey-Bloom J, Palmer B, Loreda JS, and Ancoli-Israel S. Effects of sleep disorders on the non-motor symptoms of Parkinson disease

TABLES

Table 1: Demographics

Variable	Total
N	86
Age: mean years (SD)	67.4 (8.8)
Gender: n [%]	
Male	57 [66.3]
Female	29 [33.7]
Occupation: n [%]	
Currently Working	29 [33.7]
Professional	23 [26.7]
Trade/Service	3 [3.5]
Homemaker	1 [1.2]
Other	2 [2.3]
Retired	57 [66.3]
Professional	42 [48.8]
Clerical	1 [1.2]
Trade/Service	7 [8.1]
Homemaker	4 [4.6]
Other	3 [3.5]
Income: n [%]	
<\$25,000	7 [8.1]
\$25,000 to \$49,999	13 [15.1]
\$50,000 to \$74,999	13 [15.1]
\$75,000 to \$99,999	13 [15.1]
\$100,000 to \$199,000	14 [16.3]
>\$200,000	1 [1.2]
Choose not to answer	23 [26.7]
Missing	2 [2.3]
Marital Status: n [%]	
Single	5 [5.8]
Divorced	8 [9.3]
Widowed	10 [11.6]
Married	63 [73.3]
Ethnicity/Race: n [%]	
White or Caucasian	78 [90.7]
Asian	1 [1.2]
Hispanic	5 [5.8]
Pacific Islander	1 [1.2]
Unknown	1 [1.2]
Education: n [%]	
High School Graduate	7 [8.1]
Partial College	19 [22.1]
College Graduate	18 [20.9]
Completed Graduate School	42 [48.8]

Table 2: Medical Characteristics

Variable	Total
N	86
PD Duration: mean years (SD)	6.3 (5.3)
Hoehn & Yahr: <i>n</i> [%]	
Stage I	24 [27.9]
Stage II	44 [51.1]
Stage III	12 [14.0]
Missing	6 [7.0]
UPDRS: mean (SD)	
Part 1	14.1 (6.3)
Part 2	18.5 (7.5)
Part 3	3.5 (2.3)
Total	36.1 (13.2)
Missing: <i>n</i>	6
Medications:	
LDE: mean (SD)	620.6 (478.7)
Benzodiazepine: <i>n</i> [%]	9 [10.5]
Antidepressants: <i>n</i> [%]	24 [27.9]
BMI: mean (SD)	26.8 (4.2)

Table 3: Sleep Characteristics

Variable	Total
N	86
TST: mean min (SD)	349.2 (73.3)
WASO: mean min (SD)	106.2 (62.3)
SE: mean % (SD)	74.5 (14.1)
N1 Sleep: mean % (SD)	11.7 (7.6)
N2 Sleep: mean % (SD)	60.9 (10.8)
N3 Sleep: mean % (SD)	15.7 (10.5)
REM Sleep: mean % (SD)	11.7 (7.1)
Total REM Time: mean min (SD)	43.1 (29.5)
TAI: mean number (SD)	7.1 (7.6)
%time SaO ₂ <90%: mean % (SD)	7.0 (12.9)
AHI: mean (SD)	14.1 (13.8)
PLMI: mean (SD)	21.0 (25.4)
EMGscore: mean % (SD)	12.8 (12.2)
RBDSQ: mean (SD)	5.9 (3.5)

Table 4a: Clinical and Sleep Characteristics in OSA

	OSA		
	yOSA	nOSA	p
N [%]	47 [54.7]	39 [45.3]	
Gender: Male/Female	34/13	23/16	0.19
Age: mean (SD)	68.1 (9.4)	66.6 (9.0)	0.44
PD Duration: mean years (SD)	6.0 (5.5)	6.5 (5.2)	0.67
Hoehn & Yahr: n [%]			0.64
Stage I	14 [29.8]	10 [25.6]	
Stage II	23 [48.9]	21 [53.8]	
Stage III	5 [10.6]	7 [17.9]	
Missing	5 [10.6]	1 [2.6]	
UPDRS: mean (SD)			
Part 1	13.6 (6.5)	14.6 (6.0)	0.45
Part 2	18.8 (8.1)	18.2 (6.9)	0.73
Part 3	3.0 (1.9)	4.1 (2.5)	0.02
Total	35.3 (14.1)	36.9 (12.3)	0.58
Medications:			
LDE: mean (SD)	629.5 (479.4)	609.9 (484.0)	0.85
Benzodiazepine: n[%]	6 [12.8]	3 [7.7]	0.44
Antidepressants: n[%]	12 [12.5]	12 [30.8]	0.59
BMI: mean (SD)	27.2 (4.2)	26.3 (4.2)	0.29
TST: mean min (SD)	353.3 (75.3)	344.3 (71.4)	0.57
WASO: mean min (SD)	100.8 (62.2)	112.8 (62.6)	0.38
SE: mean % (SD)	75.3 (14.6)	73.4 (13.5)	0.53
N1 Sleep: mean % (SD)	11.7 (7.7)	11.7 (7.4)	0.99
N2 Sleep: mean % (SD)	61.5 (10.2)	60.1 (11.5)	0.57
N3 Sleep: mean % (SD)	14.5 (11.0)	17.2 (9.8)	0.25
REM Sleep: mean % (SD)	12.3 (7.4)	11.0 (6.9)	0.41
Total REM Time: mean min (SD)	45.4 (30.7)	40.4 (28.0)	0.44
TAI: mean number (SD)	8.6 (8.1)	5.2 (6.6)	0.04
%time SaO2<90%: mean % (SD)	9.3 (13.0)	4.1 (12.4)	0.06
AHI: mean (SD)	22.7 (13.5)	3.7 (2.1)	<0.001
PLMI: mean (SD)	24.3 (29.2)	17.0 (19.6)	0.17
EMGscore: mean % (SD)	10.4 (9.7)	15.7 (14.3)	0.06
RBDSQ: mean (SD)	5.6 (3.6)	6.3 (3.4)	0.4

Table 4b: Clinical and Sleep Characteristics in RBD

	RBD			
	yRBD	pRBD	nRBD	p
N [%]	36 [41.9]	24 [27.9]	26 [30.2]	
Gender: Male/Female	25/11	14/10	18/8	0.63
Age: mean (SD)	67.3 (7.3)	66.6 (9.7)	68.4 (10.0)	0.77
PD Duration: mean years (SD)	6.9 (6.4)	5.7 (4.9)	5.8 (4.0)	0.62
Hoehn & Yahr: n [%]				0.99
Stage I	10 [27.8]	7 [29.2]	7 [26.9]	
Stage II	19 [52.8]	12 [50.0]	13 [50.0]	
Stage III	5 [13.9]	3 [12.5]	4 [15.4]	
Missing	2 [5.6]	2 [8.3]	2 [7.7]	
UPDRS: mean (SD)				
Part 1	15.9 (6.6)	15.1 (6.4)	10.5 (3.9)	0.003
Part 2	19.4 (7.5)	18.8 (8.5)	16.9 (6.7)	0.46
Part 3	3.5 (2.4)	3.8 (2.3)	3.3 (2.2)	0.7
Total	38.7 (13.3)	37.8 (14.4)	30.7 (10.5)	0.06
Medications:				
LDE: mean (SD)	577.8 (442.8)	671.0 (532.2)	633.4 (488.8)	0.76
Benzodiazepine: n[%]	6 [16.7]	3 [12.5]	0	0.1
Antidepressants: n[%]	9 [25.0]	11 [45.8]	4 [15.4]	0.05
BMI: mean (SD)	26.4 (3.9)	26.9 (4.5)	27.3 (4.4)	0.68
TST: mean min (SD)	358.8 (63.8)	348.6 (71.3)	336.4 (87.1)	0.5
WASO: mean min (SD)	104.3 (54.2)	99.2 (64.2)	115.3 (71.8)	0.65
SE: mean % (SD)	75.4 (12.5)	75.1 (13.6)	72.5 (16.7)	0.71
N1 Sleep: mean % (SD)	11.7 (7.4)	12.1 (9.6)	11.2 (5.7)	0.92
N2 Sleep: mean % (SD)	59.4 (10.7)	61.1 (11.1)	62.8 (10.7)	0.47
N3 Sleep: mean % (SD)	15.9 (9.7)	17.1 (12.4)	14.2 (9.8)	0.63
REM Sleep: mean % (SD)	13.1 (7.9)	9.6 (7.0)	11.8 (5.9)	0.2
Total REM Time: mean min (SD)	48.4 (31.4)	35.8 (29.4)	42.4 (26.2)	0.26
TAI: mean number (SD)	5.4 (5.8)	10.5 (9.8)	6.2 (6.7)	0.03
%time SaO ₂ <90%: mean % (SD)	4.4 (9.6)	10.7 (14.6)	7.0 (14.9)	0.18
AHI: mean (SD)	10.3 (10.9)	20.6 (18.4)	13.4 (10.7)	0.02
PLMI: mean (SD)	25.2 (27.1)	22.6 (27.1)	13.7 (20.2)	0.2
EMGscore: mean % (SD)	19.6 (11.1)	11.4 (14.3)	4.3 (2.1)	<0.001
RBDSQ: mean (SD)	8.1 (2.7)	6.5 (3.3)	2.4 (1.1)	<0.001

Table 4c: Clinical and Sleep Characteristics in RLS

	RLS		
	yRLS	nRLS	p
N [%]	19 [22.1]	67 [77.9]	
Gender: Male/Female	13/6	44/23	0.82
Age: mean (SD)	67.6 (10.3)	67.4 (8.4)	0.94
PD Duration: mean years (SD)	6.4 (6.2)	6.2 (5.1)	0.91
Hoehn & Yahr: n [%]			0.51
Stage I	4 [21.1]	20 [29.9]	
Stage II	9 [47.4]	35 [52.2]	
Stage III	4 [21.1]	8 [11.9]	
Missing	2 [10.5]	4 [6.0]	
UPDRS: mean (SD)			
Part 1	16.6 (5.0)	13.4 (6.4)	0.06
Part 2	21.2 (7.0)	17.8 (7.5)	0.09
Part 3	4.5 (1.7)	3.2 (2.4)	0.05
Total	42.3 (9.7)	34.4 (13.6)	0.02
Medications:			
LDE: mean (SD)	833.7 (509.9)	745.3 (597.0)	0.69
Benzodiazepine: n[%]	3 [15.8]	6 [9.0]	0.69
Antidepressants: n[%]	6 (31.6)	18 [26.9]	0.39
BMI: mean (SD)	27.6 (4.7)	26.6 (4.0)	0.35
TST: mean min (SD)	340.0 (75.3)	351.8 (73.1)	0.54
WASO: mean min (SD)	107.7 (53.2)	105.8 (65.0)	0.91
SE: mean % (SD)	73.6 (13.5)	74.7 (14.3)	0.77
N1 Sleep: mean % (SD)	10.2 (6.4)	12.1 (7.8)	0.34
N2 Sleep: mean % (SD)	60.3 (10.0)	61.0 (11.1)	0.8
N3 Sleep: mean % (SD)	13.3 (11.3)	14.7 (10.1)	0.09
REM Sleep: mean % (SD)	10.2 (5.4)	12.1 (7.5)	0.29
Total REM Time: mean min (SD)	37.1 (24.2)	44.8 (30.8)	0.32
TAI: mean number (SD)	8.9 (8.9)	6.5 (7.2)	0.24
%time SaO ₂ <90%: mean % (SD)	4.9 (11.0)	7.5 (13.5)	0.45
AHI: mean (SD)	11.3 (10.0)	14.9 (14.7)	0.33
PLMI: mean (SD)	17.5 (18.7)	22.0 (27.1)	0.51
EMGscore: mean % (SD)	12.8 (10.0)	12.8 (12.9)	0.99
RBDSQ: mean (SD)	6.4 (4.0)	5.8 (3.4)	0.52

Table 5a: Entire Sample Mean of NMS Questionnaires

NMS Measure	Total Sample
BDI-II	9.3 (6.4)
ESS	10.5 (4.6)
MFSI-SF	11.3 (13.3)
MoCA	24.6 (3.4)
NMSQuest	11.5 (5.2)
PDQ-39	34.7 (20.4)
PDSS	101.1 (20.8)

Table 5b: NMS Questionnaires in OSA

NMS Measure	OSA		
	yOSA	nOSA	p
BDI-II	9.6 (6.5)	9.0 (6.2)	0.32
ESS	10.8 (4.5)	10.2 (4.8)	0.34
MFSI-SF	11.7 (13.5)	10.7 (13.1)	0.62
MoCA	24.0 (3.5)	25.3 (3.2)	0.12
NMSQuest	11.4 (5.6)	11.6 (4.6)	0.95
PDQ-39	36.0 (22.0)	33.2 (18.5)	0.19
PDSS	103.2 (19.7)	98.7 (22.1)	0.42

Table 5c: NMS Questionnaires in RBD

NMS Measure	RBD			
	yRBD	pRBD	nRBD	p
BDI-II	10.6 (6.6)	10.6 (6.4)	6.5 (5.2)	0.009
ESS	10.8 (4.2)	10.6 (4.9)	10.1 (4.9)	0.93
MFSI-SF	12.1 (13.3)	16.0 (16.3)	6.0 (7.7)	0.01
MoCA	25.2 (3.3)	23.5 (3.6)	24.7 (3.3)	0.2
NMSQuest	13.1 (5.0)	11.5 (5.4)	9.2 (4.4)	0.11
PDQ-39	34.9 (20.3)	40.2 (21.7)	29.4 (18.6)	0.05
PDSS	99.2 (20.1)	93.7 (21.1)	110.7 (18.6)	0.003

Table 5d: NMS Questionnaires in RLS

NMS Measure	RLS		
	yRLS	nRLS	p
BDI-II	10.8 (5.5)	9.0 (6.5)	0.33
ESS	11.5 (5.1)	10.3 (4.5)	0.29
MFSI-SF	17.3 (14.3)	9.6 (12.5)	0.02
MoCA	23.5 (5.2)	24.9 (2.7)	0.42
NMSQuest	13.0 (4.6)	11.1 (5.3)	0.56
PDQ-39	48.7 (17.8)	30.8 (19.4)	<0.001
PDSS	92.8 (21.7)	103.5 (20.1)	0.07

Table 6: Measurement Correlational Matrix

NMS Measure	PDSS	PDQ-39	NMSQuest	NoCA	MFSI-SF	ESS
BDI-II	-0.56***	0.6***	0.68***	-0.13	0.7***	0.27*
ESS	-0.28*	0.33**	0.29**	-0.1	0.4***	-
MFSI-SF	-0.59***	0.64***	0.67***	-0.24*	-	
MoCA	0.27*	-0.14	-0.1	-		
NMSQuest	-0.61***	0.68***	-			
PDQ-39	0.69***	-				
PDSS	-					

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