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Management of sleep disorders in Parkinson's disease and Multiple System Atrophy

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Abstract

Parkinson's disease (PD) and Multiple System Atrophy (MSA) are disorders associated with α synuclein-related neurodegeneration. Non-motor symptoms are common hallmarks of these disorders, and disturbances of sleep-wake cycle are among the most common non-motor symptoms. It is only recently that sleep disturbances have received the attention of the medical and research community. Significant progress has been made in understanding the pathophysiology of sleep and wake disruption in alpha synucleinopathies over the past few decades. Despite these advancements, treatment options are limited and frequently associated with problematic side effects. Further studies that will center on development of novel treatment approaches are very much needed. In this article we review discuss current state of managements of disturbed sleep and alertness in PD and MSA.

Keywords

sleep; Parkinson's; multiple system atrophy; management

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting over one million people in United States.[1,2] Non-motor symptoms (NMS) are some of the most disabling dopa-resistant manifestations of Parkinson's disease (PD). Disrupted sleep and alertness is one of the most common NMS of PD, affecting as many as 90% of patients.[3–5] Sleep disturbances may precede motor symptoms of PD[6]; this probably reflects the degeneration of areas such as the raphe nucleus and locus coeruleus that constitute pre-clinical stages 1 and 2 of the pathological staging system proposed by Braak.[7,8]

Multiple System Atrophy (MSA) is a progressive neurodegenerative disorder characterized by parkinsonism, ataxia and autonomic dysfunction. Pathologically, MSA belongs to

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synuleinopathies and the disease process involves degeneration of striatonigral and olivopontocerebellar structures.[9] Two major categories of MSA are MSA-P with predominant parkinsonian features, and MSA-C with predominant cerebellar ataxia. Estimated prevalence of MSA is 4-5/100,000 individuals.[10]

The pathophysiology of sleep-wake disturbances in PD and MSA remains largely unknown, but the etiology is likely to be multifactorial, including: the impact of motor symptoms on sleep, adverse effects of antiparkinsonian medications, and neurodegeneration of central sleep regulatory areas.[11–18]

The most common disorders of sleep and wake in PD and MSA include insomnia, REM sleep behavior disorder (RBD), excessive daytime sleepiness (EDS), sleep disordered breathing, Restless Legs Syndrome (RLS), and circadian disruption. Disrupted sleep-wake cycles contribute to poor quality of life, impaired mood, poor cognitive performance, and increased risk for accidents, leading to increased morbidity and mortality in this population.[19–25] Current treatment options are very limited and often associated with undesirable adverse effects. There is therefore a great need to understand the mechanisms leading to sleep dysfunction in PD and MSA, and to develop new treatment modalities.

While disrupted sleep and alertness present a common and challenging problem for PD patients and their caregivers, there is a relative paucity of well-designed intervention studies primarily focused on the sleep-wake cycle in PD and MSA. This review will discuss the management of disorders of sleep and wake in PD based on reported interventional studies and available treatment guidelines for PD and MSA.

Methods

This review involved an analysis of published studies related to management of sleep dysfunction in PD and MSA included in the PubMed electronic database of the National Library of Medicine. The terms used for the search were “Parkinson’s disease”, “multiple system atrophy”, “sleep”, “management”, and “treatment”. We also examined the reference lists of relevant publications. Only original studies published in English were included in this review.

Parkinson’s disease

Insomnia

Insomnia is the most common sleep disorder in PD. Patients with PD usually do not have difficulties with falling asleep. Staying asleep, however, is very challenging for many patients, and is referred to as sleep fragmentation. Sleep fragmentation in PD can be viewed as sleep maintenance insomnia. Up to 80% of patients report sleep fragmentation and early morning awakenings.[26] It is frequently challenging to ascertain the main cause of fragmented sleep as the etiology may encompass overnight emergence of motor PD symptoms, effects of dopaminergic medications, co-existence of other primary sleep disorders, autonomic dysfunction, and the influence of primary neurodegenerative process on sleep-wake regulatory centers. Psychiatric symptoms are very common in the PD

population and have negative impact on sleep quality. Depression commonly results in early morning awakenings. This emphasizes the need for a comprehensive assessment of sleep complaints in this patient population.

Several scales have been developed to assess sleep problems in PD. Most commonly used scales are Parkinson's Disease Sleep Scale (PDSS) and the SCOPA-sleep scale.[27,28] These scales nicely complement the clinical sleep history, which is the critical step in the management. A thorough review of the medication regimen, optimization of overnight PD symptoms, management of nocturia, and treatment of overnight hallucinations and confusion may result in improved sleep consolidation. Sleep quality of the patient's caregiver should be also assessed, as his/her sleep deprivation will likely negatively affect care giving responsibilities.

Despite the overall burden of insomnia, systematic treatment guidelines and intervention studies are limited. The majority of randomized controlled trials investigating treatment of insomnia in PD in the past decade have included less than 30 patients. Approaches for the management of insomnia associated with PD include behavioral interventions and pharmacotherapy. Increased activity during the day, restriction of daytime napping, and adequate light exposure should be promoted among PD patients as these may improve consolidation of sleep-wake cycles. Proper sleep hygiene habits have to be emphasized. Cognitive behavior therapy for insomnia (CBT-I) is a potential promising line of insomnia treatment for PD patients. In a randomized, unblinded 6-week study of CBT-I combined with light therapy with 10,000 lux, significant reduction in self-reported insomnia symptoms was observed.[29] Another study of 23 PD patients employed CBT administered in 30 min telephone sessions over 3 months. The intervention resulted in improved sleep metrics captured by sleep diaries and the PDSS.[30] Further investigations of CBT-I in the PD population are warranted.

The majority of FDA-approved medications for treatment of insomnia have not been studied in the PD population. Most treatment recommendations, therefore, are based on small case-series and anecdotal reports. Generally, if pharmacotherapy for insomnia is considered necessary, medications should be used in conjunction with behavioral approaches.

Benzodiazepines are commonly prescribed for insomnia in the general population, and may cause morning sedation, confusion, and imbalance. For these reasons special caution is advised when prescribing these agents in the PD population. Eszoplicone, a non-nenzodiazepine hypnotic, was found to improve sleep quality and sleep maintenance when compared to placebo in a group of 30 PD patients with insomnia.[31] Side effects were present in 13% of patients and included EDS and dizziness.

Sedative antidepressants and antipsychotics are often prescribed for PD patients to treat co-morbid psychiatric symptoms. These medications, however, may worsen RLS, periodic limb movements, and RBD. A 12-week open-label trial of low dose quetiapine demonstrated tolerance and improvement in subjective sleep quality as measured by the Pittsburg Sleep Quality Index in a cohort of 14 PD patients.[32] Doxepin also appears to be effective for insomnia in PD patients.[29] In a 6-week study doxepin (10 mg qhs) was compared with CBT-

I + light therapy and placebo arms and resulted in improvement as measured by the Insomnia Severity Index.

Sodium oxybate is a FDA-approved treatment for narcolepsy. The medication was evaluated in an open-labeled study of PD patients and found to have significant subjective improvement in EDS and slow wave sleep duration.[33] Due to its heavy sedative properties, sodium oxybate should be used only after evaluation for sleep apnea, and not be taken with other sedative medications.

Melatonin has beneficial effects on subjective sleep quality but only mild benefit in objective sleep parameters in PD patients.[34,35] Long-term data are not available to determine whether these sleep benefits of melatonin are sustained.

Dopaminergic medications may improve overnight sleep in PD. Extended release formulation of levodopa, pramipexole, transdermal rotigotine, and prolonged release ropinirole show significant improvements in sleep quality[36–39]. These benefits appear to be modulated by improvements in overnight motor PD symptoms, but other mechanisms may be involved as well. A risk of dopamine agonist-associated EDS including sleep attacks, needs to be considered when prescribing dopaminergic therapies to improve overnight sleep.

Surgical treatments for PD, such as deep brain stimulation (DBS) may improve insomnia symptoms in PD.[40,41] Mechanisms that underlie these effects involve sleep pathways or reduction of motor symptoms. Prospective studies of effects of DBS on sleep will help determine its role in improving sleep health in the PD population.

REM Sleep Behavior Disorder

REM Sleep Behavior Disorder (RBD) is a parasomnia that precedes the onset of cardinal diagnostic features of PD and other α-synucleinopathies in over 80% of patients within 10 years of the diagnosis.[42] RBD affects approximately 50% of PD patients. Patients with akinetic/rigid phenotype, falls, higher disease severity, greater motor fluctuations, and higher levodopa dose are more likely to have co-existent RBD.[43] The presence of RBD predicts greater cognitive decline in PD. The diagnosis of RBD is based on the history of dream enactment vocal and motor behaviors in association with the loss of muscle atonia during REM sleep. REM sleep without atonia (RSWA) is the neurophysiological signature of RBD. Polysomnography (PSG) is therefore needed to establish the diagnosis of RBD, not only to demonstrate RSWA, but also to rule out mimics of RBD, such as sleep disordered breathing, other parasomnias, and nocturnal seizures. Several questionnaires have been developed for the diagnosis of probable RBD and have been utilized in clinical and research settings.[44–49]

A detailed history that encompasses the feedback from the bed partners is crucial for establishing the diagnosis of RBD. The first and most important step in the management of RBD is proper education and counseling directed to the patient and his/her caregivers. Safety measures should be implemented in order to assure maximum safety in the sleeping environment. This may include adjustments of the furniture and floor coverings, securing windows as well as removing any objects that may pose risks to injuries during dream enactment. Bed partners may need to be counseled and advised to sleep separately until

RBD is brought under control. The medication regimen has to be thoroughly reviewed and medications known to have the potential to aggravate RBD should be eliminated if at all possible. This is especially relevant to antidepressant medication that are commonly prescribed in PD and known to exacerbate symptoms of RBD.[50] Other co-existent sleep disorders should be treated, especially sleep disordered breathing that sometimes can worsen manifestations of RBD given the propensity for worsening during REM sleep and fragmented sleep. A bed alarm with accompanied reassuring message from a familiar person has been shown to be beneficial for RBD symptoms in preliminary investigations among patients with medication-refractory RBD.[51] This approach is based on a relatively low arousal threshold during REM sleep.

A threshold for initiation pharmacological therapy for RBD should be low, as potential for severe injuries is quite high. Only a few randomized controlled clinical trials for RBD have been performed to date. The evidence that guides use of pharmacotherapy in RBD is therefore based mainly on reported case series. While the most commonly prescribed medications for RBD are clonazepam and melatonin, limited data are available on the efficacy of these agents in individuals with RBD and a co-existent neurodegenerative disorder such as PD.

Clonazepam has been the most commonly used treatment for RBD. It is very efficacious in symptomatic management of RBD where up to 90% of patients report partial or complete remission of symptoms with dose range 0.5–2 mg.[52–55] The mechanism of action of clonazepam in RBD is unknown, but it appears that it reduces phasic EMG activity during REM sleep without significant effects on tonic activity. Potential problems with the use of clonazepam for RBD, especially within the PD population, include its sedative properties, which may cause excessive daytime sleepiness, predispose patients to falls overnight, or contribute to confusion.[51] Recently reported risks of cognitive decline in patients treated with benzodiazepines further emphasizes the need for caution when using this agent in PD patients who are already at risk for development of cognitive impairment with disease progression.[56] Careful surveillance of adverse events needs to be routinely performed when using clonazepam.

Several case series reported beneficial effects of melatonin for RBD with daily doses up to 12 mg.[57–59] A double-blind, placebo-controlled, cross-over trial of melatonin has been performed in 8 male patients with mild RBD.[60] Treatment with 3mg of melatonin resulted in complete resolution of dream enactment behaviors in 4/8 patients, partial resolution in 3/8 and no change in 1 patient. Study participants did not report side effects with melatonin, although morning sleepiness and headaches have been associated with melatonin use. Higher doses at melatonin at bedtime (6–15mg) augment REM atonia in association with disappearance of RBD symptoms.[60] These effects persist for weeks after the agent is discontinued. The mechanism of action of melatonin in RBD remains unknown.

Comparative efficacy of melatonin and clonazepam was assessed in a survey of 45 patients with RBD, half of whom had a co-existent neurodegenerative disorders.[61] The survey revealed effectiveness of both agents with some superiority of clonazepam. Overall, adverse events were evenly distributed among groups, while unsteadiness and dizziness were more

common in patients treated with clonazepam. The main reason for discontinuation of two agents was lack of efficacy among melatonin users and adverse events among those taking clonazepam.

A randomized, double-blind, crossover trial for RBD tested the efficacy of cholinesterase inhibitor rivastigmine in 10 patients with PD that failed treatment with melatonin and/or clonazepam.[62] Compared with placebo, 4.6mg/24 transdermal rivastigmine patch resulted in significant decrease in RBD episodes as assessed by bed-partners' reports. The efficacy of rivastigmine has been attributed to its potential effects on cholinergic system that has been implicated in the pathogenesis of RBD. Donepezil, another cholinesterase inhibitor, has also been reported to be beneficial in reducing the frequency and severity of RBD symptoms.[63]

Studies that examined efficacy of pramipexole in the treatment of RBD revealed conflicting results. Several case series documented improvements in self-reported RBD symptoms, while another series of PD patients with co-existent RBD did not find improvements in RBD events or polysomnography metrics.[64–66] In a study the examined RBD features in 11 PD patients before and three months post pramipexole treatment, no changes in RBD related symptoms and objective video-polysomnographic metrics of RBD were observed.[67] It has been speculated that pramipexole may decrease RBD behaviors by improving overall sleep fragmentation, as it does not appear to have effects on muscle activity during REM sleep.[65]

Several anectodal reports documented beneficial effects of the following in alleviating symptoms of RBD: imipramine, carbamazepine, levodopa, sodium oxybate, triazolam, zopiclone, quetiapine, and clozapine.[68] There is insufficient evidence to recommend use of these agents in the treatment of RBD. Several case series of PD patients with RBD undergoing deep brain stimulation (DBS) of the subthalamic nucleus reported little to no improvement in dream enactment or REM atonia.[69,70]

Restless Legs Syndrome

Restless legs syndrome (RLS) is a sleep related movement disorder. RLS appears to be more common in PD than in the general population and affecting approximately 20% of PD patients. Greater severity of PD, co-existent depression, and reduced serum iron binding capacity are risk factors for RLS in PD. Although both PD and RLS respond favorably to dopaminergic medications, there are no pathologic similarities between these two disorders, and no evidence that RLS progresses to PD.

Many symptoms of PD may mimic those of RLS, including wearing off symptoms, akathisia, overnight motor symptoms, or dystonic symptoms.[71] Diagnosis of RLS in PD may therefore be quite challenging even when applying well-established diagnostic criteria for RLS. This is further complicated by the fluctuating nature of PD and RLS symptoms, and overlapping medications used in the treatment of these two disorders.

Prospective treatment studies for RLS co-existent with PD are lacking. Similar to the treatment of RLS in the general population, most commonly used medications in the PD population are dopamine agonists, calcium channel alpha-2-delta ligands, clonazepam, and opioids. Dopamine agonists and levodopa are the main treatment modalities of PD and

adjustments in timing of intake of these medications may be beneficial for RLS. Levodopa, however, should be avoided as the principal medication for RLS due to risks of rebound and augmentation. Iron supplementation should be considered if ferritin levels are low. PD patients treated with clonazepam have fewer periodic limb movements (PLM) as assessed by PSG and less EDS than those not treated with clonazepam.[72] Medication known to exacerbate RLS such as dopamine blockers, anti-cholinergic and anti-histaminic agents should be discontinued if possible.

Management of augmentation is a major challenge in the treatment of RLS coexistent to PD, similar to idiopathic RLS. Augmentation manifests itself as emergence of RLS symptoms earlier in the day, increased symptoms severity, and/or shorter latency to RLS symptoms at rest. Augmentation tends to intensify with time in patients treated with dopamine agonist and levodopa. In a recent randomized, double-blind, placebo-controlled trial comparing pregabalin with pramipexole, patients receiving pregabalin had significantly reduced augmentation rate (2.1%) compared with patients treated with two doses of pramipexole (5.3% and 7.7%). Calcium channel alpha-2-delta ligands, including pregabalin therefore may be a good treatment choice for RLS in order to minimize risks of augmentation. Patients suffering from augmentation RLS may also benefit from the use of opioids as second-line treatment.[73]

DBS may modulate RLS in PD. Several studies reported favorable postoperative effects of subthalamic nucleus (STN) DBS on RLS.[74,75] This may be due to the common postoperative reductions in the dose of dopamine agonists. Emergence of RLS subsequent to STN DBS may occur as well.[76] It is therefore important to screen for RLS postoperatively as reducing dopaminergic medications may lead to emergence/unmasking of RLS in PD.

Sleep Disordered Breathing

Sleep disordered breathing (SDB) has not been extensively studied in the PD population. While initial reports of SDB reported more common prevalence in PD relative to the general population, recent studies that addressed methodological limitations of older reports found similar prevalence of SDB in PD and the general population.[77,78]

There are several features of PD-associated SDB worthy of emphasis: a) obstructive, central, and mixed apneas may be equally represented in PD; b) obesity, a strong predictor of SDB in the general population, is not predictive of this disorder in PD; c) SDB does not correlate well with self-reported and objective measures of sleepiness in PD. SDB may present as isolated EDS in individuals with PD.

There are several treatment options for SDB in PD patients, which follow the same principles of therapy for SDB in the general population. Nasal positive airway pressure therapy remains the main treatment modality for SBD in the PD population. A randomized, placebo-controlled, 6-week trial of continuous positive airway pressure therapy (CPAP) demonstrated improvements in apnea-hypopnea index, oxygen saturation, sleep continuity and daytime sleepiness.[79] Not all patients with PD tolerate CPAP well. For patients who are unable to tolerate CPAP and have milder SBD, mandibular advancement devices may be

considered. Overnight breathing problems may be improved by dopaminergic medications to reduce rigidity.[80]

Circadian Disruption

Circadian function, which has a major role in the regulation of the sleep-wake cycle, has not been systematically studies in the PD population. Emerging evidence that encompasses both basic and clinical investigations are suggestive of significant modifications of the circadian system and its implications in sleep dysfunction in PD.[81] These developments position the circadian system as a potential therapeutic target in PD and provides a platform for application of circadian-based interventions in this population. Light therapy, one of circadian-based interventions that has been routinely used in sleep medicine, shows promising outcomes on sleep and alertness in PD.

In a case series of 12 PD patients with insomnia and/or depressive symptoms, bright LT of 1000–1500 lux administered for 60–90 minutes prior to the habitual bedtime over a two-week period resulted in self-reported improved sleep onset latency, sleep continuity, and mood.[82] Beneficial effects on sleep emerged within two to three days after commencing LT, and lasted for several days after discontinuation. In an open label study, 120 PD patients were prescribed bright LT at the dose of 4000 to 6000 lux for 60 minutes prior to the habitual bedtime, and were followed from a few months to eight years.[83] Patients with good compliance reported less anxiety, improved mood and tests of motor function. In the only controlled published LT study in PD, 36 PD patients were randomized to receive bright LT with 7500 lux or placebo LT of 950 lux, for 30 minutes in the morning for two-weeks.[84] Bright LT was associated with significantly improved Unified Parkinson's Disease Rating Scale (UPDRS) part I and II scores, and modest improvements in mood and daytime sleepiness. In summary, these studies demonstrate beneficial effects of bright LT on sleep, mood and other NMS in PD. Due to limitations of these studies, mainly their relatively small size, short duration, and suboptimal design, further studies designed to test the efficacy of LT are needed.

Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) is common in the PD population and may affect up to 50% of patients.[85] The etiology is multifactorial and predisposing factors include male gender, duration and severity of PD, and the cumulative dose of dopaminergic medications. Among causes of PD-intrinsic EDS, the loss of hypocretin may be of particular importance[86], although not all studies reported alterations of the hypocretin system in patients with PD. EDS in PD has been associated with unexpected, sudden onset of sleep or "sleep attacks" that pose important safety implications.

An important and challenging aspect of EDS is the frequent lack of awareness of EDS among PD patients. This necessitates regular screening for EDS that should include input from family members/caregivers. The management of EDS in PD starts with a careful history of factors that may be contributing to the EDS. Medications regimens, especially dopaminergic medications and medications with soporific properties, have to be carefully

reviewed and adjustments made if indicated. Timely diagnosis and treatment of co-existing primary sleep disorders is critical, as these may negatively affect alertness in PD, as it does in the general population. Non-pharmacological treatment approaches can be the main approach for EDS, especially for its milder forms. Good sleep hygiene, physical activity and adequate exposure to light during daytime are important strategies for enhancing daytime alertness.

Well-designed pharmacological intervention studies directed at the treatment of EDS in PD are sparse. The most broadly studied agent for EDS on PD is modafinil. Results of several randomized controlled clinical trials revealed variable results, making conclusions about the effects of modafinil on sleepiness in PD controversial. Several studies have shown that modafinil at doses of 100 to 400 mg/d showed significant improvements in EDS as assessed by the Epworth Sleepiness Scale (ESS) and the Clinical Global Impression of Change (CGI) with a favorable side-effects profile.[87–89] Two other studies of modafinil failed to demonstrate significant improvement in the ESS.[90,91] Meta-analysis of results from four clinical trials of modafinil reveals an estimated decrease of 2.3 points on the ESS for modafinil compared with placebo.[92]

Several additional pharmacological agents have been studies for EDS in PD. In a randomized placebo-controlled double-blind trial of caffeine administered at the dose of 200 mg twice daily, sleepiness was improved as assessed by the CGI without significant improvements of the ESS score.[93] Sodium oxybate improved the ESS score and increased slow wave sleep time in an open-label study of 30 patients with PD.[33] The dose range was 2.25 g twice nightly to 4.5 g twice nightly. The medication was reasonably well tolerated and associated with mild increase in apnea-hypopnea index. Considering the overall risk profile of sodium oxybate, further studies are needed to examine the utility and safety of this medication in the PD population. Orally disintegrating selegiline has also been reported beneficial for EDS in combination with dopamine agonists.[94] Atomoxetine improves cognition and daytime sleepiness and appears to be well tolerated in PD.[95] In a small 8-week pilot study of memantine administered at 20 mg daily no improvements in sleepiness were observed.[96]

Multiple System Atrophy

Sleep disturbances are common in both MSA-P and MSA-C subtypes. Most common sleep-wake disorders are RBD, sleep fragmentation, sleep disordered breathing, and excessive daytime sleepiness. RBD is the most common sleep disorder in MSA and affects 90–100% of patients.[18] RBD and nocturnal stridor are considered red flags of the disease and have significant safety implications for patients with MSA.

Similar to PD, sleep fragmentation and reduced sleep efficiency in MSA is multifactorial, which has implications for the management of these sleep problems. Although not systematically examined in intervention studies, treatment approaches are quite similar to those applied in PD patients. Treatment of RBD in MSA also mirrors RBD associated with PD.

Sleep disordered breathing (SDB) and its management in MSA has received substantial attention. This is largely driven by its common occurrence in this patient population and by occurrence of stridor in the context of SDB that has special implications for the management of SDB in MSA. In addition to obstructive sleep apneas, central sleep apneas are also present in MSA in substantial numbers of patients.

Stridor represents upper airway obstruction and the level of glottic aperture and is characterized by high-pitched sound mainly during inspiration. Reported prevalence of stridor in MSA varies from 15–40% of patients depending on the methods of assessment.[97] Laryngoscopy is very useful in the diagnosis of stridor, and serial examination may be needed. In patients with stridor, laryngoscopic examination reveals restriction of vocal cords abduction, paradoxical cord movements, and floppy epiglottis.[98] Stridor represents a life-threatening condition as it may lead to respiratory failure. Treatment options for stridor include tracheostomy and CPAP.[99–101] Both treatments are effective; CPAP is usually considered the initial procedure of choice due to its non-invasive nature. In cases where CPAP in not well-tolerated, and if present during the daytime, trachesotomy should be the initial intervention. It has been reported that tracheostomy may increase central sleep apneas.[102] Botulinum toxin, unilateral cordectomy and laser arytenoidectomy has been proposed as treatment of MSA stridor.[103] Available evidence to support these treatments is limited. Further, the vocal cord weakness induced by botulinum toxin may predispose patients to bronchial aspiration.

Obstructive sleep apneas are common in MSA and are effectively treated with CPAP.[104] One caveat to consider in the presence of floppy epiglottis, commonly present in patients with MSA. CPAP may exacerbate upper airway obstruction in the presence of floppy epiglottis and contribute to choking that may have a fatal outcome.[105]

MSA neurodegenerative processes affect brainstem and its centers of the regulation of respiration. It is therefore not surprising that MSA patients may develop central apneas, Cheyne-Stokes respiration, apneustic breathing and respiratory pauses. In these patients CPAP therapy may not be beneficial and the use of bi-level positive airway pressure and adaptive servo ventilation (ASV) is recommended.[106]

Conclusions and Future Directions

Disruptions of sleep-wake cycles affect most patients affected by PD and MSA throughout the course of their disease. Despite this, sleep disorders associated with these synucleinopathies and other neurodegenerative disorders remain under-reported by patients and under-recognized by health care professionals. All categories of sleep disorders are associated with PD and MSA, and many have unique aspects when present that likely reflects the interaction of PD- and MSA-specific neurodegeneration with mechanisms regulating sleep and alertness. While there is substantial overlap in the types of sleep disorders encountered across PD and MSA, certain sleep disorders are either unique to, or far more prevalent in PD and MSA, which provide clues to the unique pathophysiology of each disorder.

The majority of the therapeutic recommendations for sleep disorders in the PD and MSA populations are based on open-label small clinical series or case reports. Further research should focus on better understanding of the pathophysiological mechanisms underlying sleep dysfunction and EDS in PD and MSA. Prospective studies of the development and natural history of sleep disorders in these disorders are also needed. These research efforts will inform design and execution of double-blind, placebo-controlled clinical trials with a large number of patients that are necessary in order to establish the efficacy and safety of therapeutic interventions aimed at the treatment of sleep dysfunction in PD and MSA. This will require a collaborative and multidisciplinary approach of clinicians and investigators involved in various aspects of movement disorders, sleep medicine and neurology.

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Table 1

Treatment strategies for sleep-wake disturbances associated with PD and MSA.

Sleep disorder	Treatment
Insomnia	Optimize control of overnight PD motor symptoms Review and adjust medication regimen Recognize and treat co-existent primary sleep disorders Recognize and treat co-existent psychiatric comorbidities Recognize and treat autonomic dysfunction associated with PD Provide education about sleep hygiene Implement behavioral interventions (e.g., cognitive-behavior therapy) Light therapy Pharmacological intervention: Eszopiclone Quetiapine Doxepin Sodium-oxybate Melatonin Dopaminergic medications
REM Sleep Behavior Disorder	Provide education how to enhance safety in the sleep environment Provide counseling to the patient and bed-partner about potential injurious behaviors in the context of RBD Pharmacological intervention: Melatonin Clonazepam Rivastigmine
Restless Legs Syndrome	Calcium channel alpha-2-delta ligands Dopamine agonists Clonazepam Opioids
Sleep disordered breathing	Nasal positive airway pressure therapy (nPAP) Weight loss (if applicable) Promoting sleep in non-supine positions Dental appliance Consultation with an ENT specialist Tracheotomy (for nPAP resistant stridor)
Excessive sleepiness	Review and adjust medication regimen Recognize and treat co-existent primary sleep disorders Recognize and treat co-existent psychiatric comorbidities Light therapy Pharmacological intervention: Modafinil Methylphenidate Caffeine