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REVIEW

Sleep Issues in Parkinson's Disease and Their Management

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Abstract

Parkinson's disease (PD) is an alpha-synucleinopathy that leads to prominent motor symptoms including tremor, bradykinesia, and postural instability. Nonmotor symptoms including autonomic, neurocognitive, psychiatric symptoms, and sleep disturbances are also seen frequently in PD. The impact of PD on sleep is related to motor and nonmotor symptoms, in addition to the disruption of the pathways regulating sleep by central nervous system pathology. Rapid eye movement sleep behavior disorder is a parasomnia that can lead to self-injury and/or injury to partners at night. Restless legs syndrome is a subjective sensation of discomfort and urge to move the legs prior to falling asleep and can lead to insomnia and reduced sleep quality. Excessive daytime sleepiness is common in PD and exerts a negative impact on quality of life in addition to increasing the risk of falls. Obstructive sleep apnea is a breathing disorder during sleep that can cause frequent awakenings and excessive daytime sleepiness. Circadian rhythm dysfunction can lead to an advanced or delayed onset of sleep in patients and create disruption of normal sleep and wake times. All of these disorders are common in PD and can significantly reduce sleep quantity, sleep quality, or quality of life for patients and caretakers. Treatment approaches for each of these disorders are distinct and should be individualized to the patient. We review the literature regarding these common sleep issues encountered in PD and their treatment options.

Key Words Parkinson's disease · SLEEP · insomnia · rapid eye movement sleep behavior disorder (RBD) · restless legs syndrome (RLS) · excessive daytime sleepiness (EDS) · obstructive sleep apnea (OSA) · circadian rhythm disorder

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that is typically characterized by progressive rest tremor, bradykinesia, rigidity, and gait instability. Nonmotor features including impaired olfaction, constipation, nocturia, neuropsychiatric symptoms, and sleep disturbances are also common and can precede the clinical diagnosis of PD by many years [1, 2]. Sleep complaints experienced by patients, however, appear to be underdiagnosed. Although 80% of patients with PD experience sleep disturbances, as many as 30% will not discuss it with their healthcare providers [3, 4]. Sleep disturbances can result from nocturnal motor and nonmotor symptoms, including tremor, painful dystonia, and nocturia [1, 2, 5]. In addition, neurodegeneration of the sleep control centers in the brainstem and diencephalon as well as iatrogenic factors may explain the high prevalence of a number of sleep disorders. These include insomnia, restless legs syndrome (RLS), rapid eye movement sleep behavior disorder (RBD), excessive daytime sleepiness (EDS), obstructive sleep apnea (OSA), and circadian rhythm disturbances [2, 6, 7]. All these disorders can potentially lead to reduced sleep quality, in addition to objective changes on PSG such as increased sleep latency, and reductions in total sleep time and N3 sleep [2, 6, 8, 9]. Identification and treatment of these sleep issues is paramount given the negative impact they have on quality of life [1, 2]. Here, we review the treatment options for common sleep issues encountered in PD.

Insomnia

Insomnia is defined as difficulty with initiating sleep, maintaining sleep and awakening earlier than desired for at least 3 days per week over 3 months [10]. Sleep fragmentation is

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most common in PD, occurring in up to 81% of patients, while increased latency of sleep onset appears to occur much less frequently [10]. Insomnia can present as a primary disorder and may even predate onset of motor symptoms in PD [3, 6]. This is suspected to result from neurodegeneration of various sleep-wake centers in the brainstem, such as locus coeruleus, raphe nucleus, and pedunculopontine nucleus [3]. More commonly, insomnia may result from a combination of motor and nonmotor symptoms in PD or from other sleep disorders such as RLS and OSA. The latter will be discussed later in this review.

Insomnia is a clinical diagnosis that does not require a polysomnography unless another sleep disorder is suspected and has been increasingly recognized as a negative influence on quality of life in PD [10, 11]. Various questionnaires have been developed to identify specific nocturnal PD symptoms that may contribute to insomnia, as well as to measure the effect of treatment. The Parkinson's Disease Sleep Scale (PDSS) can be used to identify nocturnal symptoms that may occur in PD, as well as subjective measures of sleep quality [12]. Individual questions include tremor, immobility in bed, and dystonia, as well as nocturia and hallucinations. The PDSS-2 is a revised version that includes a severity scale and specific questions regarding restlessness, tremor, and cramping [13]. The NMS Questionnaire is a 30-item comprehensive questionnaire that assesses multiple motor and nonmotor domains, including sleep dysfunction [14]. While not validated specifically for assessing sleep in PD, many of the domains evaluated by this questionnaire (urinary and mood disturbances) also occur at night and can disrupt sleep [14]. As insomnia typically results from underlying symptoms of PD or sleep disorders, treatment should be focused on these issues to improve sleep disruption.

Insomnia and Motor Symptoms of PD

Nocturnal motor symptoms of PD frequently contribute to insomnia and can occur in over 60% of patients [15]. This includes symptoms of tremor, dystonia, akinesia, and restlessness. One study evaluated a cohort of 412 patients with PD, 209 of whom (51%) had trouble with initiation of sleep or fragmentation during the 5-year study [11]. Motor fluctuations of tremor and rigidity were significantly associated with difficulty falling asleep, obtaining too little sleep and awakening too early in this study. Immobility in bed due to hypokinesia from PD has also been associated with an increased wake after sleep onset [16]. One study evaluated nocturnal mobility in patients with PD by using an accelerometer and number of turnover movements in bed [17]. Turnover movements were negatively correlated with increasing disease duration, levodopa equivalent daily dose, modified Hoehn and Yahr ratings, and UPDRS III scores ($p < 0.05$) [17]. This would suggest that sleep dysfunction due to motor symptoms is not as prominent early in or with a less severe disease state.

Treatment of nocturnal motor symptoms in PD does not differ significantly from standard care for daytime motor symptoms. However, most strategies employ use of long-acting medications to last throughout the night [18]. Controlled-release carbidopa-levodopa administered at bedtime has demonstrated improvements in nocturnal akinesia, though objective measures of sleep did not significantly improve [18, 19]. Extended release forms of dopamine agonists have also been studied. The effect of rotigotine on nocturnal and early morning motor fluctuations in PD was evaluated via PDSS-2 questionnaires and was found to significantly improve overnight tremor and dystonia, as well as ability to fall asleep ($p < 0.05$) [13]. The benefit of rotigotine has since been corroborated by actigraphy- and polysomnography-based evaluations in patients with PD, with notable improvement in objective sleep measures [20, 21]. Similarly, a long-acting form of ropinirole and immediate-release pramipexole have both been shown to significantly improve overall PDSS scores when added as adjunctive therapy to levodopa in patients with significant sleep difficulties at night [22, 23]. Sustained-release pramipexole has also demonstrated benefit on sleep compared to the immediate release form in a head-to-head trial, with a 6.8-point difference in the mean PDSS score at 18 weeks that trended toward significant ($p = 0.16$) [24]. The monoamine oxidase B inhibitor rasagiline was also evaluated using the PDSS and was shown to improve nocturnal tremor and restlessness in patients with PD [25]. Furthermore, patients reported a significantly improved ability to fall asleep and reduction of nocturnal awakenings in patients when rasagiline was used as adjunctive therapy ($p < 0.01$) [25]. Selection of the specific medication used should be individualized to the patient, though it appears that most long-acting oral and transdermal medications for PD are effective in reducing motor symptoms that disrupt sleep.

Finally, deep brain stimulation (DBS) for motor fluctuations in PD has also shown to improve sleep. Early DBS trials did not specifically evaluate measures of sleep as a primary outcome, but total sleep time was shown to increase by nearly an hour in each trial [26–28]. Later studies have since utilized the PDSS and PDSS-2 to demonstrate a significant improvement in tremor, akinesia, and dystonia up to 3 years after implantation [29–31]. Although the exact mechanism by which DBS improves sleep in PD remains unclear, this is most likely mediated by improvement of motor and possibly nonmotor symptoms [32]. Deep brain stimulation should not be used specifically to treat sleep issues in PD, and standard guidelines for treatment of motor fluctuations in PD should be followed.

Insomnia and Nonmotor Symptoms of PD

Nonmotor features of PD can also be disruptive of sleep. These include such symptoms as nocturia and mood disturbances [10, 18]. Nocturia is a disruptive symptom that may be caused by detrusor muscle overactivity from autonomic dysfunction in PD [33]. Roughly 35% of patients with PD suffer from this symptom and are awakened frequently throughout the night as a result [18]. An aforementioned study which demonstrated 209 of 412 patients with PD suffered from insomnia found that urinary symptoms significantly contributed to difficulty falling asleep and multiple awakenings [11]. One recent study administered the SCOPA-AUT, a measure of dysautonomia in PD, and found that a higher score in patients with PD was positively correlated with questions evaluating poor sleep on both the PDSS-2 and NMS questionnaire [34]. Treatment of nocturia may focus initially on behavioral interventions, such as reduction of fluid intake in the evening and adjustment of diuretic agents to the morning. However, nocturia can remain a significant issue and may require pharmacologic intervention. Use of such medications as solifenacin, trospium, and mirabegron can be used in PD due to their selective activity in the bladder and low side effect profile compared to anticholinergics used for this issue [33]. Solifenacin, a muscarinic inhibitor with minimal CNS penetration, has been prospectively studied for urinary dysfunction in PD and was found to significantly reduce the total number of urinary incontinence and nocturia episodes over a 24-h period ($p < 0.05$) [35]. Trospium is another antimuscarinic commonly prescribed for urinary issues in PD, but this has not been specifically evaluated in this population. However, limited evidence in a cognitively impaired population suggests it does not worsen cognition and may be used safely in these groups [36]. In a retrospective analysis, the B3 agonist mirabegron at a dose of 50 mg was found to significantly reduce nocturia episodes in PD (3.0 to 2.6 per 24-h period) [37]. Although these medications have been shown to be beneficial in PD, their use as monotherapy may not be sufficient to control nocturia. In these cases, a referral to a urologist is recommended for treatment with other medications including botulinum toxin administration to the bladder [33]. Evaluation and treatment of comorbid conditions such as prostate hypertrophy may also be helpful in reducing urinary symptoms [33].

Depression and anxiety affect between 30 and 60% of PD patients and appear to result from neurotransmitter changes as the disease progresses [5, 38]. Although early research suggested that decreases in dopamine and norepinephrine were involved in the development of depression in PD, recent literature suggests that serotonin plays a more prominent role [38, 39]. The presence of poor sleep and mood disturbances appears to have a reciprocal relationship, with the presence of one appearing to worsen the other [40–42]. One study evaluated 98 patients with and without PD using the Insomnia Severity Index (ISI) and Beck Depression Inventory to measure the impact of insomnia on depression [43]. Total sleep time in patients with PD appeared to have a greater correlation with depression severity than that in controls which could reflect a synergistic effect of depression and PD on sleep duration ($p < 0.05$) [43].

Treatment of insomnia due to mood disturbances in PD has recently focused on nonpharmacologic therapies for both issues given their interaction. Cognitive behavioral therapy (CBT) has been the gold standard of therapy for insomnia in all populations, and recently has been shown as effective in PD. In an early study, use of CBT significantly reduced ISI scores in patients with PD compared to placebo ($n = 12$; $p < 0.05$) [44]. Improvements in total sleep time, sleep latency, and sleep efficiency have been demonstrated in follow-up CBT studies for PD and were sustained for 3 months post-intervention [45–47]. Results from these small studies are promising, though larger follow-up studies are needed. Bright light therapy administered in the morning has been evaluated in a small sample size and was not shown to be beneficial in patients with PD, anxiety, and insomnia [48]. Various exercise programs have been shown to be helpful in improving sleep. One controlled study demonstrated that subjective sleep quality improved in patients with PD after participation in a 12-week resistance training program compared to non-exercisers [49]. Another controlled trial showed significant improvement in subjective sleep quality, sleep efficiency, and total sleep time in PD patients assigned to high-intensity exercise training compared to non-exercise controls ($p < 0.01$) [50].

In persistent insomnia from mood disorders refractory to other interventions, pharmacotherapy is recommended for treatment of the underlying mood disturbance [51]. However, most antidepressants with the exception of bupropion can exacerbate rapid eye movement sleep behavior disorder and restless legs syndrome, both common in patients with PD [52, 53]. Commonly used insomnia medications have rarely been studied in the PD population and evidence for pharmacologic treatment is extrapolated from non-PD populations. Chronic use of benzodiazepine and benzodiazepine receptor agonists may lead to cognitive decline and dementia in non-PD populations [54]. However, a limited course of benzodiazepine receptor agonists or melatonin receptor agonist has been recommended over most other sedative hypnotics for treatment of insomnia [55, 56]. Doxepin is a pure histamine blocker (H1) at doses less than 10 mg and has been recommended for treatment of insomnia due to a relatively favorable safety profile in the elderly with no clear risk of abuse or dependence [55, 57]. Suvorexant is a dual orexin receptor antagonist also considered safe for use in the elderly with insomnia [57]. A pooled analysis from five trials comparing suvorexant to placebo in the elderly showed no

additional risk of falls and no effect on morning psychomotor performance [58]. A slightly higher rate of reported residual somnolence was seen in the suvorexant 15 mg group compared to controls (5.4% vs. 3.2%) [58].

Insomnia in PD may result from a combination of motor, nonmotor, and mood symptoms. Treatment should focus on the underlying issue, with most patients requiring multiple treatment modalities depending on the stage of disease (Fig. 1). For those with insomnia and comorbid mood disorders, nonpharmacologic interventions such as CBT and exercise appear to have significant benefit on subjective and objective sleep. Pharmacologic treatments may also be used with some caution. Long-term use of benzodiazepine and benzodiazepine receptor agonists should be avoided given a potential risk of cognitive decline with chronic use, while doxepin and suvorexant appear to be efficacious with limited side effects in non-PD populations.

Rapid Eye Movement Sleep Behavior Disorder

Rapid eye movement sleep behavior disorder (RBD) is a parasomnia that arises out of REM sleep and leads to a loss of paralysis of skeletal muscles where patients may exhibit dream enactment behavior [59]. These behaviors during sleep may range from mild muscle twitches to vocalizations to violent and complex motor behaviors. This can lead to falling out of bed, self-injury, or injury to bed partners [60]. In fact, bed partners may be the first to note these types of complex behaviors during sleep, as patients themselves are unaware of most episodes [53]. The prevalence of RBD is estimated to be 0.5–1% of the general population, but up to 50% in the PD population [53, 60, 61]. A diagnosis of probable RBD can be made clinically based on the presence of nocturnal behaviors associated with vivid or violent dreams [60]. A definitive diagnosis requires polysomnography (PSG) confirmation of abnormal tonic elevation and/or bursts of muscle tone measured by electromyography (EMG), termed "loss of REM atonia" [60]. The underlying mechanism leading to loss of REM atonia in PD is likely mediated by accumulation of alpha-synuclein in pontine nuclei such as the sublaterodorsal nucleus and ventral medial medulla, which send inhibitory projections to the spinal motor neurons during REM sleep [62–65]. For a number of patients with PD, the symptoms of RBD precede motor manifestations and a formal diagnosis of PD by a median time of 10 years, providing an opportunity for early diagnosis and neuroprotective interventions [66–69].

Investigation into treatment of RBD has been somewhat limited, as prospective evaluations of medications or supplements are lacking. Unfortunately, most studies do not specifically evaluate PD populations, so data is extrapolated from "isolated RBD" or iRBD populations. First-line intervention should include evaluation of environmental safety. Bed rails can be recommended to reduce the risk of falling from bed, as well as removal of dangerous weapons in or near the patient's bedroom [70, 71]. The potential for injury to the patient and/or bed partner, however, should quickly prompt initiation of therapy to reduce this risk [70, 71]. Serotonergic medications commonly used for other symptoms in PD, such as depression and anxiety, can notoriously precipitate or worsen symptoms

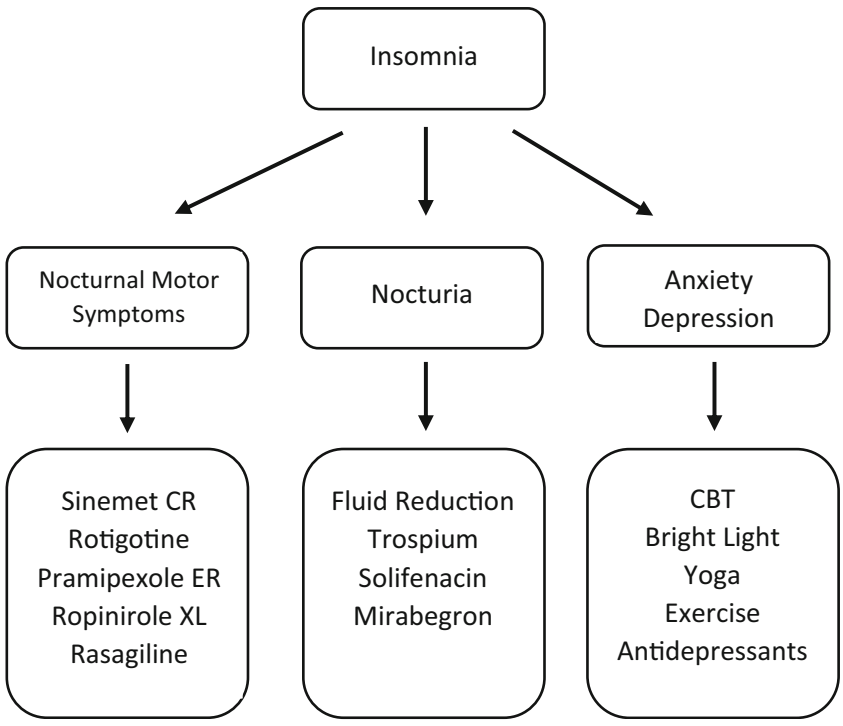

Fig. 1 Treatment flow chart for insomnia in Parkinson's disease (PD). Motor symptoms from PD such as tremor, dystonia, and rigidity can contribute to insomnia. The treatment of nocturnal symptoms typically employs long-acting forms of antiparkinsonian medication to last through a night of sleep. Nocturia is a symptom of PD that can significantly disrupt sleep and may be treated with behavioral modification and medications with low side effect profiles. Mood disturbances commonly contribute to insomnia and may be treated with a combination of nonpharmacologic measures and antidepressant medication

of RBD [52]. These include selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants [52, 72]. Other agents that can worsen RBD include antipsychotics, barbiturates, alcohol, and caffeine [72]. Reduction or discontinuation of these agents are recommended to reduce their impact on RBD. Finally, "Pseudo-RBD" can be seen in the presence of untreated OSA, which can lead to agitated arousals following obstructive events [73]. Diagnosis and subsequent treatment of OSA with CPAP in a patient with comorbid RBD is paramount to help reduce nocturnal behaviors [74].

The most widely used pharmacologic treatments for RBD are clonazepam and melatonin. Clonazepam has been the most studied treatment for RBD, with the bulk of evidence for its use based on retrospective case series in the iRBD population [71]. More recently, clonazepam has been evaluated in a prospective fashion. Fifteen patients with iRBD were studied on clonazepam and compared via PSG and RBD severity scales to 42 patients with untreated iRBD [75]. While clonazepam increased total sleep times and decreased wakefulness after sleep onset compared to controls, the percentage of REM atonia was not significantly different between the two groups [75]. RBD severity scores on clonazepam did not significantly change from baseline to a mean follow-up of 2.6 years [75]. Another open-label study following 39 patients on clonazepam for more than 2 years found that 67% had complete elimination of sleep-related injuries and potentially injurious behaviors to self and/or bed partners [76]. However, the only RCT using clonazepam in patients with RBD and PD failed to show superiority over placebo. This 4-week trial in 40 patients with probable RBD treated with fixed 0.5-mg dose of clonazepam or placebo showed no difference between groups based on the Clinical Global Impressions-Improvement (CGI-I) scores [77]. This could be due to methodological issues as suggested by a high responder rate in the placebo group. In addition, doses of clonazepam higher than 0.5 mg may be more effective based on observational studies and anecdotal evidence.

Similar to clonazepam, early evidence for use of melatonin was based on case series. One such series evaluated 14 RBD patients with various neurodegenerative disorders and their response to melatonin [78]. Melatonin doses from 3 to 12 mg appeared to be effective as monotherapy or adjunctive therapy with clonazepam for controlling RBD or markedly improving it per patient and caregiver report [78]. The first and only RCT supporting melatonin was a double-crossover placebo-controlled trial in 8 patients with iRBD over 4 weeks [79]. Interestingly, significant improvement of REM atonia was seen on PSG in the melatonin group ($p = 0.012$) [79], which was sustained for several weeks. Notable restoration of atonia during REM on PSG was also demonstrated in a similar study [80]. However, two subsequent RCTs using 2–4 mg of extended release melatonin were unable to show superiority over placebo [81, 82]. Other studies have since evaluated the melatonin receptor agonist ramelteon, though results are mixed [83, 84].

Other medications have been evaluated for treatment of RBD with limited success or applicability of results due to small study sizes. The rationale for acetylcholinesterase inhibitors is based on empiric evidence that the presence of RBD in PD is associated with cholinergic denervation [85]. Two crossover placebo-controlled trial evaluated rivastigmine in patients with RBD. The first trial evaluated patients with PD and PSG-confirmed RBD who failed clonazepam or melatonin and showed that use of a 4.6-mg patch for 3 weeks significantly reduced the mean frequency of RBD episodes from 4 to 2 episodes per month, whereas no change was observed in the placebo condition [86]. The second trial in patients with MCI and refractory RBD yielded similar results, with an effect size of about 50% in the rivastigmine group [87]. A few case reports showed inconsistent response to donepezil in patients with Lewy body dementia (LBD) [88, 89]. An RCT of 42 patients evaluated memantine 20 mg or placebo in patients with PD or DLB [90]. Results suggested a reduction in nocturnal movement and/or vocalizations per caregivers after 24 weeks compared to baseline; however, no formal clinical evaluation of RBD was performed in this study. In addition, only about half of the participants exhibited motor/vocal activity at baseline in the memantine group and even less in the placebo group. Pramipexole was studied in 15 patients with iRBD where a 50% reduction of nighttime behaviors was seen in 80% of subjects, while PSG demonstrated lower REM density after treatment [91]. This is in contrast with earlier studies that did not show improvement on PSG [92]. There is a case series suggesting use of gabapentin as adjunctive therapy for iRBD when added to clonazepam and/or melatonin [93]. Finally, sodium oxybate has been used when other therapies failed, with some success in four case reports of patients with and without PD [94–96]. A trial to investigate use of this medication in patients with RBD is currently underway (NCT04006925).

Current evidence suggests that clonazepam and melatonin should continue to be used as first-line agents to treat RBD in PD (Fig. 2). Melatonin is favored due to its favorable side effect profile, while addition of clonazepam can be considered in refractory cases. Second-line treatments could include rivastigmine, donepezil, dopaminergic agents, or sodium oxybate in more severe cases (Fig. 2).

Restless Legs Syndrome

Restless leg syndrome (RLS) is a common sleep disorder found in patients with PD with a prevalence estimated to range from 8 to 24% [9, 97–99]. The diagnosis of RLS requires four criteria: (1) the urge to move one's extremities due to severe

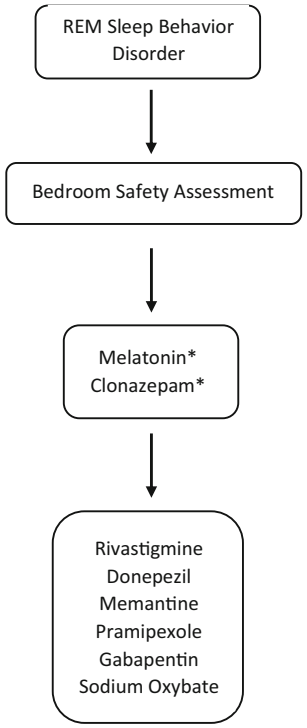

Fig. 2 Treatment flow chart for rapid eye movement behavior disorder (RBD) in Parkinson's disease (PD). First-line therapies for RBD include an assessment of bedroom safety, followed by melatonin and clonazepam. Melatonin is preferred given a lower side effect profile. Second-line and experimental therapies include cholinesterase inhibitor medications, memantine, gabapentin, pramipexole, and sodium oxybate, though evidence is limited for all of these agents. *Suggested first-line therapies

discomfort or pain (a subset of patients may also experience symptoms in their arms or back); (2) the urge starts or worsens during periods of rest; (3) the urge can occur throughout the day but is worse during the evening or night; (4) the urge is decreased or relieved by movement [97]. Recently, a fifth criteria was added to state that the above features should not be solely accounted for by another medical or behavioral condition, such as myalgias or leg cramps [97]. This is particularly important in PD as patients may experience nocturnal symptoms of restlessness or tremor that may mimic RLS. These symptoms are not typically relieved by movement, which can help to differentiate between nocturnal motor symptoms of PD and RLS [97].

The underlying pathophysiology of RLS is poorly understood, but recent investigation suggests that central nervous system (CNS) iron levels are reduced in patients with RLS [100, 101]. Medications used for treatment of motor and nonmotor symptoms in PD can also worsen RLS. These include antidepressants with serotonergic activity and antihistamines [102, 103]. Although some studies suggest that RLS may be an early neurological symptom in PD, others have found that RLS incidence is not increased before initiation of PD treatment [104–107]. In the latter studies, RLS appears to increase over time and correlate with the duration of PD [106, 107].

Treatment of RLS in PD is both behavioral and pharmacological. Conservative measures such as avoidance of alcohol or caffeine, as well as mild to moderate exercise, may be used as an initial approach to treatment [102]. Reduction or cessation of offending medications such as serotonergic antidepressants should be approached cautiously given the high rates of comorbid depression and anxiety, but can also help reduce symptoms [102, 103]. If ferritin levels are < 75 ng/ml and/or transferrin saturation index < 20%, oral ferrous sulfate 325 mg with vitamin C has been recommended [108, 109]. In cases where oral supplementation is not tolerated or a rapid response is needed, infusions of 1 g of iron dextran or ferrous carboxymaltose in two separate doses 1 week apart can be beneficial. Clinical improvement can be expected in 50–60% of patients and, interestingly, is often delayed by 3–5 weeks [108]. However, iron therapy has not been studied in the PD population and it remains to be seen if oral or intravenous supplementation is beneficial [110].

If the above measures have not provided sufficient relief, pharmacologic management is recommended. The majority of studies evaluating pharmacologic treatment of RLS are in non-PD populations. As a result, recommendations for treatment in the PD population are extrapolated from this data. These studies use the International Restless Legs Syndrome Study Group rating scale (IRLS) to assess severity of symptoms, where 0–10 is mild, 11–20 is moderate, 21–30 is severe, and 31–40 is very severe. Dopamine agents such as ropinirole, pramipexole, and rotigotine have the most evidence for use in RLS based on multiple RCTs [102, 110, 111]. Ropinirole was compared to placebo in patients with at least severe RLS (40-point International restless legs scale score $\geq$ 24; IRLS). Although both groups experienced improvements in total IRLS scores, the ropinirole group had a lower IRLS score of 2.1 points than placebo at 26 weeks, demonstrating its effectiveness for RLS ($p < 0.05$) [112]. Similarly, a recent double-blind RCT demonstrated superiority of pramipexole over placebo in reducing RLS severity [113]. At 12 weeks, pramipexole significantly reduced the mean IRLS score compared to placebo by a difference of 3.8 points ($p < 0.01$) [113]. This corroborated an earlier study which demonstrated the same difference in IRLS scores after 12 weeks of treatment with pramipexole compared to placebo [114]. Rotigotine appears to improve RLS symptoms similar to other dopamine agonists. A double-blind RCT found that IRLS scores were significantly lower on a 2-mg or 3-mg rotigotine patch compared to placebo after 6 months of treatment ($p < 0.001$) [115]. Similar results have been produced in another RCT [116]. Levodopa has also been used for treatment of RLS with good results, though much of evidence supporting its use is based on early case series and randomized controlled trials that do not employ the IRLS scale [117, 118]. A meta-analysis of

levodopa use in RLS demonstrated a significant improvement of RLS severity compared to placebo using CGI-I ($p < 0.0001$), confirming its efficacy in the short term [118]. Interestingly, there was clinically significant improvement of RLS symptoms with placebo in many of the above trials which highlights the suggestibility of this disorder. However, these same studies have demonstrated effectiveness of dopamine agents compared to placebo and established them as first-line agents [109, 111].

Though effective for RLS treatment, there are multiple issues with chronic use of dopamine agonists. First, they often result in "augmentation" of RLS. This is when symptoms no longer respond and are paradoxically worsened by treatment, occur earlier in the day, and/or spread to previously unaffected body parts [111, 119, 120]. This often leads to an increase in dopaminergic medications, triggering further augmentation. As RLS is considered a "hyperdopaminergic state," dopaminergic drugs that target the inhibitory dopamine D3 receptor are initially effective [121]. However, long-term use of dopaminergic agonists results in upregulation of the excitatory D1 receptor, also seen with aging, which is suspected to lead to augmentation [121]. Levodopa may cause augmentation in over 80% of patients based on early case series, while pramipexole and ropinirole may lead to this at a rate up to 10% per year [111, 122, 123]. This data on augmentation has only been studied in non-PD RLS populations, however, limiting applicability to the PD population with RLS. Nevertheless, we recommend caution when using dopaminergic treatment for RLS in PD populations. These agents are often used for treatment of motor symptoms in PD at higher doses than those typically used for RLS and may increase risk of augmentation.

Secondly, dopaminergic treatments lead to impulse control disorders (ICDs) in about 10–15% patients with PD [124]. This can manifest as pathologic gambling, impulsive shopping, sexual behaviors, and eating. In addition, those who experience augmentation appear to have a six-times-higher risk of developing ICDs [124]. This elevated risk is likely related to use of dopaminergic treatment but may also represent an underlying tendency of RLS patients to develop ICDs [124]. Although patients with PD were not included in this study, risk of developing ICDs is elevated in PD for similar reasons and should prompt caution when using dopamine agents in this group [125]. Strategies to minimize the risk of augmentation and/or ICDs include utilizing long-acting dopamine agonists or shifting to other first-line agents for RLS [109, 111, 119, 120].

Alpha-2-delta ligand agents (pregabalin, gabapentin, and gabapentin enacarbil) are now considered first-line therapy and are effective in reducing RLS symptoms [102, 109, 111, 119, 120]. Gabapentin acts via binding at the alpha-2-delta subunit of the voltage-gated calcium channel, which reduces release of excitatory neurotransmitters, including glutamate [119, 120, 126]. However, use of gabapentin in RLS is based on early case series with limited number of patients [119, 120, 126]. Gabapentin enacarbil, a prodrug and controlled-release form of gabapentin, has since been shown to be superior to placebo for reduction of RLS symptoms in multiple double-blind RCTs [111]. A study that evaluated three of these trials found gabapentin enacarbil 600 mg to be significantly effective in reducing RLS severity after 12 weeks of treatment compared to placebo [127]. All other doses up to 2400 mg were also effective at reducing RLS severity ($p < 0.01$). Pregabalin is the third drug available in this class. In a large placebo-controlled trial, pregabalin was compared to two doses of pramipexole (0.25 mg and 0.5 mg) over 12 weeks and found to be effective at reducing RLS severity compared to baseline [128]. No significant differences in efficacy were found between pregabalin and the higher dose of pramipexole, while less augmentation was seen with pregabalin in this study at 52 weeks (pregabalin 1.7%; pramipexole 0.25 mg 6.6%; pramipexole 0.5 mg 9.0%). These agents do not have a significant risk of augmentation and should be considered for initial RLS therapy in patients with PD as a result [128].

Opiates have also been shown to be effective for reducing RLS severity, but are generally reserved for those who have failed other agents or augmentation that has been reticent to other therapies [111, 119, 126, 129]. As this has not been studied in PD populations, use of opiates should be considered with extreme caution, if not avoided altogether due to risk of sedation and respiratory depression. Finally, benzodiazepines were previously used for treatment of RLS, but have fallen out of favor given insufficient evidence, as well as a side effect profile similar to opiates [109, 111].

The impact of DBS on RLS in patients with PD has also been evaluated. One prospective study evaluated 31 PD patients with STN DBS who did not have RLS at baseline [130]. Six patients developed RLS symptoms at 6 months after DBS [130]. Post-operatively, these patients were on a higher mean dopamine equivalent dose than those without RLS, suggesting DBS either unmasked RLS symptoms or that the development of RLS represented augmentation [130]. More recently, a prospective trial of 22 PD patients with STN DBS demonstrated that RLS scores significantly improved after 2 years of DBS, despite a mean reduction in dopaminergic medications [131]. No correlation was found between RLS severity and reduction in PD medications, suggesting that STN DBS may have mediated this improvement [131]. It is unclear if reduction in medication improved pre-existing augmentation. Though research in this area is conflicting, the most recent evidence suggests that STN DBS in PD may help with RLS symptoms in the long term.

Treatment of RLS in PD should begin with nonpharmacologic measures, but often requires use of medication due to severity of symptoms (Fig. 3). The choice of therapy for RLS in PD should be tailored to the individual

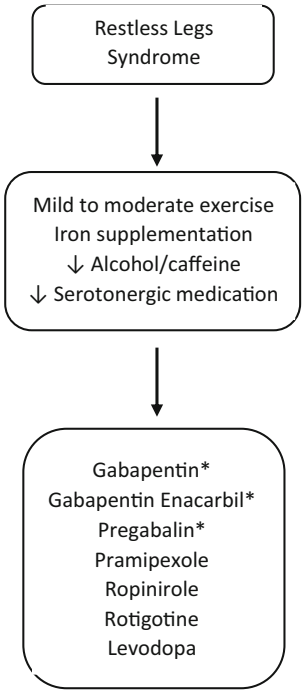

Fig. 3 Treatment flow chart for restless legs syndrome (RLS) in Parkinson's disease (PD). Although behavioral modifications are recommended as primary interventions, these measures are often inadequate for reduction in severity of RLS symptoms. First-line therapies for RLS include alpha-2-delta ligand agents such as pregabalin, gabapentin enacarbil, and gabapentin. Second-line agents include dopaminergic medications commonly used for treatment of PD, but should be used with caution. These are associated with higher rates of augmentation, a paradoxical worsening of RLS symptoms directly related to their use. *Suggested first-line therapies

patient with an understanding that problematic side effects from long-term dopamine agonist use can occur. Although we suggest alpha-2-delta ligand agents as first-line therapy for treatment of RLS in PD as monotherapy or in combination with other agents, dopaminergic medications are also effective for treatment of both RLS and motor symptoms of PD. While the latter may be used in an attempt to limit polypharmacy and treat multiple symptoms at once, we recommend these with caution as they may create augmentation and increase the risk of ICDs. Opiates should generally be avoided in the PD population.

Excessive Daytime Sleepiness in PD

Excessive daytime sleepiness (EDS) is a common symptom in PD and can occur anywhere from 15 to 21% early in the disease course and up to 46% as the disease progresses [132–135]. A study of early and untreated PD showed that EDS may be related to disease progression and is independent of other sleep disorders, while others have shown that dopaminergic medication appears to increase EDS in a dose-dependent fashion [132–134, 136]. Some studies have also suggested an association of EDS in PD with depression [133, 137, 138]. Interestingly, patients with PD and EDS appeared to have reduced uptake in the basal ganglia on dopaminergic terminal imaging compared to those without EDS [133, 139]. The PD and EDS groups also have worse scores on motor, nonmotor, autonomic, and cognitive testing [133, 139]. This suggests that more severe disease could be a contributing factor to development of EDS, in addition to dopamine medication levels [133, 135].

The presence of EDS negatively impacts quality of life in PD. One study evaluated 198 patients with PD using the Parkinson's Disease Questionnaire 39 (PDQ-39), a measure of quality of life [132]. This study demonstrated that those with PD and EDS had a significantly lower overall score on the PDQ-39 than those without EDS ($p < 0.001$), as well as individual emotional, social, and physical domains measured by this survey ($p < 0.01$). EDS in PD also represents an additional risk of falling. One study evaluated 120 patients with PD and found that every point increase on the Epworth Sleepiness Scale (ESS) was associated with a 20% higher risk of falling ($p < 0.01$) [140].

Because of the negative impact that EDS has on quality of life in PD, identification and treatment is important. The Epworth Sleepiness Scale (ESS) is a 24-point scale used to identify individuals with sleepiness, with a score of greater than 10 indicating excessive daytime sleepiness. Many studies have used this as primary endpoint to evaluate changes in daytime sleepiness. One such trial evaluated 31 patients with PD and EDS (defined by an ESS greater than 12) using bright light as an intervention [141]. After 2 weeks, bright light therapy administered from 9 to 11 a.m. and 5–7 p.m. demonstrated significant improvements in the ESS compared to the control group. Interestingly, the ESS remained with a nearly 4-point improvement after intervention and 2-week washout period in the PD group, as well as a 2-point improvement sustained in the control group, suggesting a prolonged effect of bright light therapy. Another trial ($n = 61$) evaluated the use of caffeine in patients with EDS in PD [142]. Patients were titrated on caffeine up to 200 mg twice daily over 6 weeks, with a lower ESS of 1.7 point at endpoint compared to the control group. The caffeine group, however, began with a higher ESS score (15.4) at baseline compared to the controls (14.6), which may have led to a larger decrease in ESS.

Multiple RCTs have evaluated the use of the stimulant modafinil for EDS in PD with mixed results. One crossover study demonstrated a significant reduction in ESS with modafinil up to 200 mg daily compared to placebo in 12 patients with PD and an ESS greater than 10 [143]. This was corroborated by a similar study which showed that modafinil 200 mg significantly improved ESS

compared to placebo [144]. However, a larger follow-up study ($n = 40$) did not find that modafinil up to 400 mg significantly reduced ESS, though a mean reduction in ESS of 2.7 was seen after 4 weeks of treatment [145]. Sodium oxybate, FDA approved for treatment of narcolepsy, has been investigated for EDS in PD. Twelve patients titrated from 3 to 9 mg demonstrated significant improvements in ESS (mean reduction 4.2) and improvements in sleep latency and slow-wave sleep duration ($p < 0.01$) [146].

One study evaluated the effect of istradefylline, a selective adenosine A2A receptor antagonist, in 21 patients with EDS in PD [147]. ESS scores were significantly reduced after 3 months of use in patients on up to 40 mg of istradefylline daily ($p < 0.0001$) [147]. Other medications such as bupropion and dextroamphetamine have been suggested as possible treatments; however, there are no published data evaluating these agents [148].

Although treatments for EDS are limited, bright light therapy and caffeine have low side effect profiles and are easy to implement, supporting their use as initial steps for treatment (Fig. 4). Other treatment options are considered experimental at this time. Patients with EDS from a suspected underlying sleep disorder should undergo additional evaluation and treatment, as outlined in other parts of this article.

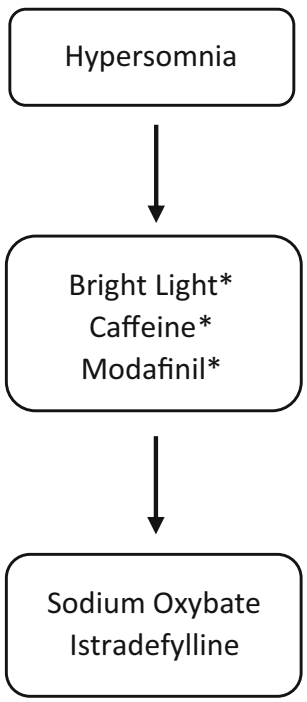

Fig. 4 Treatment flow chart for hypersomnia in Parkinson's disease (PD). First-line therapies for hypersomnia include the use of bright light and caffeine, as well as the stimulant modafinil. Other medications such as sodium oxybate and istradefylline are considered experimental at this time. Other sleep disorders that may contribute to hypersomnia should also be ruled out and treated.*Suggested first-line therapies

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a common condition that results in repeated reduction of the airflow during the night due to anatomical obstruction of the airway [149]. Presence of this disorder may result in daytime sleepiness, fatigue, and cognitive impairment, all of which are issues encountered in PD due to the disease itself or medications used to treat it [149, 150]. Although some studies have suggested an increased prevalence of OSA in PD due to stiffness and difficulty with turning in bed, a recent meta-analysis demonstrated that there may be a lower risk of OSA in PD [149–151]. Patients with PD and RBD may also experience lower rates of OSA, possibly due to a protective effect of enhanced muscle tone during REM sleep [152]. However, a more recent case-control study ($n = 3194$) evaluated 194 patients with PD with PSG and found significantly higher rates of OSA compared to controls ($p < 0.05$) [149]. Elevated body mass index was not associated with the severity of OSA in PD in this study, unlike the general population. It did suggest that alteration of the laryngopharyngeal motor control may be a distinct mechanism contributing to OSA in PD.

Obstructive sleep apnea can lead to various cardiovascular and neurologic consequences with negative impact on the quality of life in patients with PD [149, 153]. Specifically, repeated hypoxemic events from OSA may contribute to CNS inflammation and oxidative injury, both of which can contribute to cognitive dysfunction [153]. While one study ($n = 92$) found that patients with PD and OSA did not appear to have worsening of motor or nonmotor features of PD, other studies have demonstrated poorer cognition in PD with OSA than PD without OSA based on Mini Mental Status Examination (27.45 v. 28.41; $p < 0.05$) and Montreal Cognitive Assessment testing (24.00 v. 25.29; $p < 0.05$) [154–156]. In addition, RBD appears to increase the risk of cognitive impairment in PD and OSA, furthering the notion that RBD represents a more malignant phenotype of PD [152].

Despite the negative impact of OSA on cognition in PD, studies evaluating treatment have yielded mixed results. One study evaluating the impact of controlled-release levodopa/carbidopa on the severity of OSA in PD patients showed a trend toward reduction of the apnea-hypopnea index (AHI) in the treatment group, though the difference was not statistically significant [155]. Gold standard treatment of OSA is continuous positive airway pressure (CPAP). Use of CPAP for OSA in PD has been shown to significantly improve objective measures such as the AHI and nocturnal oxygenation [157]. In addition, daytime sleepiness also appears to significantly improve in this population [157]. Unfortunately, CPAP has yet to demonstrate significant benefit for cognitive difficulties in those with PD and OSA [155, 158]. A comparison of therapeutic versus placebo CPAP in PD patients with OSA significantly improved AHI after 3 weeks of treatment ($p = 0.01$).

However, there were no significant differences in either the composite or 13 individual neuropsychological tests in both groups [158]. A limitation of this study is the length of follow-up, as it may take longer treatment with CPAP to produce improvement in cognition. However, long-term use of CPAP may be difficult in this group due to motor and cognitive issues, with socio-economic status a possible influence on adherence rates [158]. Nevertheless, adherence to CPAP in patients with PD and OSA should be addressed and may help with daytime sleepiness, as well as reduce the risk of other medical comorbidities. On a case-by-case basis, other treatment options include positional therapy to promote sleep in a non-supine position, custom-made mandibular advancement devices, optimization of nasal breathing, etc.

Circadian Rhythm Disorders

Alteration of the circadian rhythm is common in PD. The circadian rhythm is a roughly 24-h cycle that regulates physiologic and behavioral processes [6, 10]. In healthy individuals, this rhythm allows for the alternance of sleep and wake as continuous, prolonged, and well-demarcated phases that align with an individual's social and/or professional demands, as well as preference [6, 10]. This alignment is coordinated by the suprachiasmatic nucleus (SCN) and can be entrained by a number of *zeitgebers* (timegivers) such as melatonin, food intake, physical exercise, and light. Circadian rhythm disorders arise when these endogenous (biological) and exogenous (social, professional) rhythms are misaligned. This can lead to significant changes in sleep and wake times, often creating off-setting sleep schedules between patients and caretakers [6]. In PD, disruption of the circadian rhythm can be due to a number of factors [6, 10]. Pathologic changes in both the SCN and its afferents originating in the photosensitive retinal ganglion cells in PD patients have been noted in histologic studies [159, 160]. Additionally, reduced mobility in PD contributes to reduced exposure to outdoor light, an important influence on the circadian rhythm [161]. Dopaminergic medications may also negatively impact the circadian rhythm by reducing melatonin secretion, which rises during the early evening hours preceding sleep in healthy subjects [6, 10, 162]. Blunting of this peak in secretion has been demonstrated in small groups of patients with PD on dopamine medications, while dopamine-naïve patients did not have this same response [162, 163].

Although the evidence specifically evaluating the treatment of circadian rhythm disorders in PD is limited, interventions that have shown to be effective in other clinical situations can be helpful in this patient population. A recent RCT showed that 10,000-lux bright light therapy in the morning and early evening can reduce excessive daytime sleepiness, sleep fragmentation, and insomnia and improve mood in patients with PD [141]. Light therapy has also shown to improve motor function [164]. Other chronotherapies including physical exercise and melatonin may be beneficial but have not been systematically evaluated in patients with PD.

Conclusion

Sleep in PD appears to be disrupted through a number of mechanisms. Difficulty with sleep onset and maintenance in PD may result from motor features such as tremor and dystonia, as well as nonmotor features including nocturia. Other sleep disorders such as RLS or RBD can also occur and negatively impact quality of life for both the patient and caretaker. Careful questioning can lead to early identification of these sleep disturbances, many of which do not require a PSG for diagnosis.

Treatment of these sleep disturbances often requires a multifaceted approach which depends on the specific issue. Motor and nonmotor features that lead to insomnia often require pharmacologic adjustment for treatment, though CBT can be effective in mood disorders that lead to insomnia. Treatment of RLS may first start with behavioral adjustments such as avoidance of caffeine and alcohol, while alpha-2-delta ligands and dopaminergic agents have been shown to be effective in multiple RCTs. Development of augmentation and ICDs in the latter group of medications should be assessed for frequently. REM sleep behavior disorder requires adjustment of the bedroom environment for safety reasons as well as initiation of melatonin as a first-line agent. Other than clonazepam, little evidence exists for use of other medications to treat RBD. Obstructive sleep apnea requires a PSG for diagnosis, while treatment with CPAP can improve daytime sleepiness. Circadian rhythm disorders may be more common in PD than previously thought, leading to late sleep times and increasing the risk of daytime sleepiness. Investigation of treatment in PD specifically is limited, but light therapy in the morning and early evening appears to be a promising first-line intervention.

References

1. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR, Group NV. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. Mov Disord. 2011;26:399–406.
2. Gómez-Esteban JC, Tijero B, Somme J, et al. Impact of psychiatric symptoms and sleep disorders on the quality of life of patients with Parkinson's disease. J Neurol. 2011;258(3):494-9.
3. Dhawan V, Healy DG, Pal S, Chaudhuri KR. Sleep-related problems of Parkinson's disease. Age Ageing. 2006;35(3):220-8.
4. Hurt CS, Rixon L, Chaudhuri KR, Moss-Morris R, Samuel M, Brown RG. Barriers to reporting non-motor symptoms to health-

care providers in people with Parkinson's. Parkinsonism Relat Disord. 2019;64:220-225.
5. Hermanowicz N, Jones SA, Hauser RA. Impact of non-motor symptoms in Parkinson's disease: a PMDAlliance survey. Neuropsychiatr Dis Treat. 2019;15:2205-2212.
6. Mantovani S, Smith SS, Gordon R, O'Sullivan JD. An overview of sleep and circadian dysfunction in Parkinson's disease. J Sleep Res. 2018;27(3):e12673.
7. Videnovic A. Management of sleep disorders in Parkinson's disease and multiple system atrophy. Mov Disord. 2017;32(5):659-668.
8. Rolinski M, Szewczyk-Krolikowski K, Tomlinson PR, et al. REM sleep behaviour disorder is associated with worse quality of life and other non-motor features in early Parkinson's disease. J Neurol Neurosurg Psychiatry. 2014;85(5):560-6.
9. Rijsman RM, Schoolderman LF, Rundervoort RS, Louter M. Restless legs syndrome in Parkinson's disease. Parkinsonism Relat Disord. 2014;20 Suppl 1:S5-9.
10. Gros P, Videnovic A. Sleep and Circadian Rhythm Disorders in Parkinson's Disease. Curr Sleep Med Rep. 2017 Sep;3(3):222-234.
11. Zhu K, van Hilten JJ, Marinus J. The course of insomnia in Parkinson's disease. Parkinsonism Relat Disord. 2016; 33:51-57.
12. Chaudhuri KR, Pal S, DiMarco A, et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease.J Neurol Neurosurg Psychiatry. 2002;73(6):629-35.
13. Trenkwalder C, Kohnen R, Högl B, et al. Parkinson's disease sleep scale–validation of the revised version PDSS-2. Mov Disord. 2011;26(4):644-52.
14. Romenets SR, Wolfson C, Galatas C, et al. Validation of the non-motor symptoms questionnaire (NMS-Quest). Parkinsonism Relat Disord. 2012; 18(1):54-8.
15. Muntean ML, Benes H, Sixel-Döring F, et al. Clinically relevant cut-off values for the Parkinson's Disease Sleep Scale-2 (PDSS-2): a validation study. Sleep Med. 2016;24:87-92.
16. Louter M, van Sloun RJ, Pevernagie DA, et al. Subjectively impaired bed mobility in Parkinson disease affects sleep efficiency. Sleep Med. 2013; 14(7):668-74.
17. Uchino K, Shiraishi M, Tanaka K, Akamatsu M, Hasegawa Y. Impact of inability to turn in bed assessed by a wearable three-axis accelerometer on patients with Parkinson's disease. PLoS One. 2017;12(11):e0187616.
18. Loddo G, Calandra-Buonaura G, Sambati L, et al. The Treatment of Sleep Disorders in Parkinson's Disease: From Research to Clinical Practice. Front Neurol. 2017;8:42.
19. Wailke S, Herzog J, Witt K, Deuschl G, Volkmann J. Effect of controlled-release levodopa on the microstructure of sleep in Parkinson's disease. Eur J Neurol. 2011; 18(4):590-6.
20. Pierantozzi M, Placidi F, Liguori C, et al. Rotigotine may improve sleep architecture in Parkinson's disease: a double-blind, randomized, placebo-controlled polysomnographic study. Sleep Med. 2016; 21:140-4.
21. Calandra-Buonaura G, Guaraldi P, Doria A, et al. Rotigotine Objectively Improves Sleep in Parkinson's Disease: An Open-Label Pilot Study with Actigraphic Recording. Parkinsons Dis. 2016; 2016:3724148.
22. Ray Chaudhuri K, Martinez-Martin P, Rolfe KA, et al. Improvements in nocturnal symptoms with ropinirole prolonged release in patients with advanced Parkinson's disease. Eur J Neurol. 2012; 19(1):105-13.
23. Poewe WH, Rascol O, Quinn N, et al. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. Lancet Neurol. 2007; 6(6):513-20.
24. Xiang W, Sun YQ, Teoh HC. Comparison of nocturnal symptoms in advanced Parkinson's disease patients with sleep disturbances: pramipexole sustained release versus immediate release formulations. Drug Des Devel Ther. 2018;12:2017-2024.
25. Schettino C, Dato C, Capaldo G, Sampaolo S, Di Iorio G, Melone MA. Rasagiline for sleep disorders in patients with Parkinson's disease: a prospective observational study. Neuropsychiatr Dis Treat. 2016 Sep 29;12:2497-2502.
26. Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med. 2010;362(22):2077-91.
27. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA. 2009;301(1):63-73.
28. Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med. 2013;368(7):610-22.
29. Kurcova S, Bardon J, Vastik M, et al. Bilateral subthalamic deep brain stimulation initial impact on nonmotor and motor symptoms in Parkinson's disease: An open prospective single institution study. Medicine (Baltimore). 2018;97(5):e9750.
30. Choi JH, Kim HJ, Lee JY, et al. Long-term effects of bilateral subthalamic nucleus stimulation on sleep in patients with Parkinson's disease. PLoS One. 2019;14(8):e0221219.
31. Deli G, Aschermann Z, Ács P, et al. Bilateral Subthalamic Stimulation can Improve Sleep Quality in Parkinson's Disease. J Parkinsons Dis. 2015;5(2):361-8.
32. Sharma VD, Sengupta S, Chitnis S, Amara AW. Deep Brain Stimulation and Sleep-Wake Disturbances in Parkinson Disease: A Review. Front Neurol. 2018;9:697.
33. Sakakibara R, Panicker J, Finazzi-Agro E, et al. A guideline for the management of bladder dysfunction in Parkinson's disease and other gait disorders. Neurourol Urodyn. 2016; 35(5):551-63.
34. Matsubara T, Suzuki K, Fujita H, et al. Autonomic Symptoms Correlate with Non-Autonomic Non-Motor Symptoms and Sleep Problems in Patients with Parkinson's Disease. Eur Neurol. 2018;80(3-4):193-199.
35. Zesiewicz TA, Evatt M, Vaughan CP, et al. Randomized, controlled pilot trial of solifenacin succinate for overactive bladder in Parkinson's disease. Parkinsonism Relat Disord. 2015;21(5): 514-20.
36. Orme S, Morris V, Gibson W, Wagg A. Managing Urinary Incontinence in Patients with Dementia: Pharmacological Treatment Options and Considerations. Drugs Aging. 2015;32(7):559-67.
37. Peyronnet B, Vurture G, Palma JA, et al. Mirabegron in patients with Parkinson disease and overactive bladder symptoms: A retrospective cohort. Parkinsonism Relat Disord. 2018;57:22-26.
38. Poewe W. Non-motor symptoms in Parkinson's disease. Eur J Neurol. 2008;15 Suppl 1:14-20.
39. Butala A, Shepard M, Pontone G. Neuropsychiatric aspects of Parkinson disease psychopharmacology: Insights from circuit dynamics. Handb Clin Neurol. 2019;165:83-121.
40. Rana AQ, Qureshi ARM, Shamli Oghli Y, et al. Decreased sleep quality in Parkinson's patients is associated with higher anxiety and depression prevalence and severity, and correlates with pain intensity and quality. Neurol Res. 2018;40(8):696-701.
41. Rutten S, Vriend C, van der Werf YD, Berendse HW, Weintraub D, van den Heuvel OA. The bidirectional longitudinal relationship between insomnia, depression and anxiety in patients with early-stage, medication-naïve Parkinson's disease. Parkinsonism Relat Disord. 2017;39:31-36.
42. Palmeri R, Lo Buono V, Bonanno L, et al. Potential predictors of quality of life in Parkinson's Disease: Sleep and mood disorders. J Clin Neurosci. 2019;70:113-117.

43. Kay DB, Tanner JJ, Bowers D. Sleep disturbances and depression severity in patients with Parkinson's disease. Brain Behav. 2018;8(6):e00967.
44. Rios Romenets S, Creti L, Fichten C, et al. Doxepin and cognitive behavioural therapy for insomnia in patients with Parkinson's disease – a randomized study. Parkinsonism Relat Disord. 2013;19(7):670-5.
45. Patel S, Ojo O, Genc G, et al. A Computerized Cognitive behavioral therapy Randomized, Controlled, pilot trial for insomnia in Parkinson Disease (ACCORD-PD). J Clin Mov Disord. 2017;4: 16.
46. Humbert M, Findley J, Hernandez-Con M, Chahine LM. Cognitive behavioral therapy for insomnia in Parkinson's disease: a case series. NPJ Parkinsons Dis. 2017;3:25.
47. Lebrun C, Gély-Nargeot MC, Rossignol A, Geny C, Bayard S. Efficacy of cognitive behavioral therapy for insomnia comorbid to Parkinson's disease: A focus on psychological and daytime functioning with a single-case design with multiple baselines. J Clin Psychol. 2019 20.
48. Raymackers JM, Andrade M, Baey E, Vanneste M, Evrard F. Bright light therapy with a head-mounted device for anxiety, depression, sleepiness and fatigue in patients with Parkinson's disease. Acta Neurol Belg. 2019;119(4):607-613.
49. Silva-Batista C, de Brito LC, Corcos DM, Roschel H, de Mello MT, Piemonte MEP, Tricoli V, Ugrinowitsch C. Resistance Training Improves Sleep Quality in Subjects With Moderate Parkinson's Disease. J Strength Cond Res. 2017;31(8):2270-2277.
50. Amara AW, Wood KH, Joop A, Memon RA, Pilkington J, Tuggle SC, Reams J, Barrett MJ, Edwards DA, Weltman AL, Hurt CP, Cutter G, Bamman MM. Randomized, Controlled Trial of Exercise on Objective and Subjective Sleep in Parkinson's Disease. Mov Disord. 2020;35(6):947-958.
51. Seppi K, Ray Chaudhuri K, Coelho M, et al. Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. Mov Disord. 2019;34(2):180-198.
52. McCarter SJ, St Louis EK, Sandness DJ, et al. Antidepressants Increase REM Sleep Muscle Tone in Patients with and without REM Sleep Behavior Disorder. Sleep. 2015;38(6):907-17.
53. Zhang X, Sun X, Wang J, Tang L, Xie A. Prevalence of rapid eye movement sleep behavior disorder (RBD) in Parkinson's disease: a meta and meta-regression analysis. Neurol Sci. 2017;38(1):163-170.
54. de Gage Billioti S, Moride Y, Ducruet T, et al. Benzodiazepine use and risk of Alzheimer's disease: case-control study. BMJ. 2014;349:g5205.
55. Gooneratne NS, Vitiello MV. Sleep in older adults: normative changes, sleep disorders, and treatment options. Clin Geriatr Med. 2014;30(3):591-627.
56. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2015;63(11):2227-46.
57. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2016;165(2):125-33.
58. Herring WJ, Connor KM, Snyder E, et al. Suvorexant in Elderly Patients with Insomnia: Pooled Analyses of Data from Phase III Randomized Controlled Clinical Trials. Am J Geriatr Psychiatry. 2017;25(7):791-802.
59. Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. Sleep. 1986;9(2):293-308.
60. Boeve BF. REM sleep behavior disorder: Updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions. Ann N Y Acad Sci. 2010;1184:15.
61. Fernández-Arcos A, Iranzo A, Serradell M, Gaig C, Santamaria J. The Clinical Phenotype of Idiopathic Rapid Eye Movement Sleep Behavior Disorder at Presentation: A Study in 203 Consecutive Patients. Sleep. 2016;39(1):121-32.
62. Saper CB. The neurobiology of sleep. Continuum (Minneap Minn). 2013;19(1 Sleep Disorders):19-31.
63. Iranzo A. The REM sleep circuit and how its impairment leads to REM sleep behavior disorder. Cell Tissue Res. 2018 Jul;373(1): 245-266.
64. Boeve BF, Dickson DW, Olson EJ, et al. Insights into REM sleep behavior disorder pathophysiology in brainstem-predominant Lewy body disease. Sleep Med. 2007;8(1):60-4.
65. Postuma RB, Adler CH, Dugger BN, et al. REM sleep behavior disorder and neuropathology in Parkinson's disease. Mov Disord. 2015;30(10):1413
66. Högl B, Stefani A, Videnovic A. Idiopathic REM sleep behaviour disorder and neurodegeneration - an update. Nat Rev Neurol. 2018;14(1):40-55.
67. Arnaldi D, Antelmi E, St Louis EK, Postuma RB, Arnulf I. Idiopathic REM sleep behavior disorder and neurodegenerative risk: To tell or not to tell to the patient? How to minimize the risk?. Sleep Med Rev. 2017;36:82-95.
68. Iranzo A, Fernández-Arcos A, Tolosa E, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. PLoS One. 2014;9(2):e89741.
69. Galbiati A, Verga L, Giora E, Zucconi M, Ferini-Strambi L. The risk of neurodegeneration in REM sleep behavior disorder: A systematic review and meta-analysis of longitudinal studies. Sleep Med Rev. 2019;43:37-46.
70. Jung Y, St Louis EK Treatment of REM Sleep Behavior Disorder. Curr Treat Options Neurol. 2016;18(11):50.
71. Aurora RN, Zak RS, Maganti RK, et al. Best Practice Guide for the Treatment of REM Sleep Behavior Disorder (RBD). J Clin Sleep Med. 2010; 6(1): 85–95.
72. Teman PT, Tippmann-Peikert M, Silber MH, Slocumb NL, Auger RR. Idiopathic rapid-eye-movement sleep disorder: associations with antidepressants, psychiatric diagnoses, and other factors, in relation to age of onset. Sleep Med. 2009;10(1):60-5.
73. Bugalho P, Mendonça M, Barbosa R, Salavisa M. The influence of sleep disordered breathing in REM sleep behavior disorder. Sleep Med. 2017;37:210-215.
74. Gabryelska A, Roguski A, Simpson G, Maschauer EL, Morrison I, Riha RL. Prevalence of obstructive sleep apnoea in REM behaviour disorder: response to continuous positive airway pressure therapy. Sleep Breath. 2018;22(3):825-830.
75. Ferri R, Marelli S, Ferini-Strambi L, et al. An observational clinical and video-polysomnographic study of the effects of clonazepam in REM sleep behavior disorder. Sleep Med. 2013;14(1):24-9.
76. Li SX, Lam SP, Zhang J, et al. A prospective, naturalistic follow-up study of treatment outcomes with clonazepam in rapid eye movement sleep behavior disorder. Sleep Med. 21 (2016) 114–120.
77. Shin C, Park H, Lee WW, Kim HJ, Kim HJ, Jeon B. Clonazepam for probable REM sleep behavior disorder in Parkinson's disease: A randomized placebo-controlled trial. J Neurol Sci. 2019;401:81-86.
78. Boeve BF, Silber MH, Ferman TJ. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. Sleep Med. 2003;4(4):281-4.

79. Kunz D, Mahlberg R. A two-part, double-blind, placebo-controlled trial of exogens melatonin in REM sleep behaviour disorder. J Sleep Res. 2010;19(4):591-6.
80. McGrane IR, Leung JG, St Louis EK, Boeve BF. Melatonin therapy for REM sleep behavior disorder: a critical review of evidence. Sleep Med. 2015;16(1):19-26.
81. Jun JS, Kim R, Byun JI, et al. Prolonged-release melatonin in patients with idiopathic REM sleep behavior disorder. Ann Clin Transl Neurol. 2019;6(4):716-722.
82. Gilat M, Coeytaux Jackson A, Marshall NS, et al. Melatonin for Rapid Eye Movement Sleep Behavior Disorder in Parkinson's Disease: A Randomised Controlled Trial. Mov Disord. 2019 31.
83. Nomura T, Kawase S, Watanabe Y, Nakashima K. Use of ramelteon for the treatment of secondary REM sleep behavior disorder. Intern Med. 2013;52(18):2123-6.
84. Esaki Y, Kitajima T, Koike S, et al. An Open-Labeled Trial of Ramelteon in Idiopathic Rapid Eye Movement Sleep Behavior Disorder. J Clin Sleep Med. 2016;12(5):689-93.
85. Kotagal V, Albin RL, Müller ML, et al. Symptoms of rapid eye movement sleep behavior disorder are associated with cholinergic denervation in Parkinson disease. Ann Neurol. 2012;71(4):560-8.
86. Di Giacopo R, Fasano A, Quaranta D, Della Marca G, Bove F, Bentivoglio AR. Rivastigmine as alternative treatment for refractory REM behavior disorder in Parkinson's disease. Mov Disord. 2012;27(4):559-61.
87. Brunetti V, Losurdo A, Testani E, et al. Rivastigmine for refractory REM behavior disorder in mild cognitive impairment. Curr Alzheimer Res. 2014;11(3):267-73.
88. Ringman JM, Simmons JH. Treatment of REM sleep behavior disorder with donepezil: a report of three cases. Neurology. 2000;55(6):870-1.
89. Massironi G, Galluzzi S, Frisoni GB. Drug treatment of REM sleep behavior disorders in dementia with Lewy bodies. Int Psychogeriatr. 2003;15(4):377-83.
90. Larsson V, Aarsland D, Ballard C, Minthon L, Londos E. The effect of memantine on sleep behaviour in dementia with Lewy bodies and Parkinson's disease dementia. Int J Geriatr Psychiatry. 2010;25(10):1030-8.
91. Sasai T, Inoue Y, Matsuura M. Effectiveness of pramipexole, a dopamine agonist, on rapid eye movement sleep behavior disorder. Tohoku J Exp Med. 2012;226(3):177-81.
92. Kumru H, Iranzo A, Carrasco E, et al. Lack of effects of pramipexole on REM sleep behavior disorder in Parkinson disease. Sleep. 2008;31(10):1418-21.
93. Abenza Abildúa MJ, Miralles Martinez A, Arpa Gutiérrez FJ, et al. Conditions associated with REM sleep behaviour disorder: Description of a hospital series. Neurologia. 2017.
94. Shneerson JM. Successful treatment of REM sleep behavior disorder with sodium oxybate. Clin Neuropharmacol. 2009;32(3): 158-9.
95. Liebenthal J, Valerio J, Ruoff C, Mahowald M. A Case of Rapid Eye Movement Sleep Behavior Disorder in Parkinson Disease Treated With Sodium Oxybate. JAMA Neurol. 2016;73(1):126-7.
96. Moghadam KK, Pizza F, Primavera A, Ferri R, Plazzi G. Sodium oxybate for idiopathic REM sleep behavior disorder: a report on two patients. Sleep Med. 2017;32:16-21.
97. Allen RP, Picchietti DL, Garcia-Borreguero D, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria–history, rationale, description, and significance. Sleep Med. 2014;15(8):860-73.
98. Trenkwalder C, Allen R, Högl B, Paulus W, Winkelmann J. Restless legs syndrome associated with major diseases: A systematic review and new concept. Neurology. 2016 ;86(14):1336-43.
99. Bhalsing K, Suresh K, Muthane UB, Pal PK. Prevalence and profile of Restless Legs Syndrome in Parkinson's disease and other neurodegenerative disorders: a case-control study. Parkinsonism Relat Disord. 2013;19(4):426-30.
100. Earley CJ, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. Neurology. 2000;54(8):1698-700.
101. Daubian-Nose P, Frank MK, Esteves AM. Sleep disorders: a review of the interface between restless legs syndrome and iron metabolism. Sleep Sci 2014;7:234–7.
102. Silber MH, Becker PM, Earley C, Garcia-Borreguero D, Ondo WG. Medical Advisory Board of the Willis-Ekbom Disease Foundation. Willis-Ekbom Disease Foundation revised consensus statement on the management of restless legs syndrome. Mayo Clin Proc 2013;88:977–86.
103. Ondo WG. Common comorbidities and differential diagnosis of restless legs syndrome. J Clin Psychiatry 2014;75:e06.
104. Wong JC, Li Y, Schwarzschild MA, Ascherio A, Gao X. Restless legs syndrome: an early clinical feature of Parkinson disease in men. Sleep. 2014;37(2):369-72.
105. Szatmari S Jr, Bereczki D, Fornadi K, Kalantar-Zadeh K, Kovesdy CP, Molnar MZ. Association of Restless Legs Syndrome With Incident Parkinson's Disease. Sleep. 2017 1;40(2).
106. Angelini M, Negrotti A, Marchesi E, Bonavina G, Calzetti S. A study of the prevalence of restless legs syndrome in previously untreated Parkinson's disease patients: absence of co-morbid association. J Neurol Sci. 2011;310(1-2):286-8.
107. Lee JE, Shin HW, Kim KS, Sohn YH. Factors contributing to the development of restless legs syndrome in patients with Parkinson disease. Mov Disord. 2009;24(4):579-82.
108. Allen RP, Picchietti DL, Auerbach M, et al. Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report. Sleep Med. 2018;41:27-44.
109. Garcia-Borreguero D, Kohnen R, Silber MH, et al. The long-term treatment of restless legs syndrome/Willis-Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. Sleep Med 2013;14:675–84.
110. De Cock Cochen V. Therapies for Restless Legs in Parkinson's Disease. Curr Treat Options Neurol. 2019;21(11):56.
111. Winkelman JW, Armstrong MJ, Allen RP, et al. Practice guideline summary: Treatment of restless legs syndrome in adults: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2016;87(24):2585-2593.
112. Giorgi L, Asgharian A, Hunter B. Ropinirole in patients with restless legs syndrome and baseline IRLS total scores ≥ 24: efficacy and tolerability in a 26-week, double-blind, parallel-group, placebo-controlled study followed by a 40-week open-label extension. Clin Ther. 2013; 35(9):1321-36.
113. Zhang J, Liu B, Zheng Y, Chu T, Yang Z. Pramipexole for Chinese people with primary restless legs syndrome: a 12-week multicenter, randomized, double-blind study. Sleep Med 2015;16: 181–185.
114. Ferini-Strambi L, Aarskog D, Partinen M, et al. Effect of pramipexole on RLS symptoms and sleep: a randomized, double-blind, placebo-controlled trial. Sleep Med 2008;9:874–881.
115. Hening WA, Allen RP, Ondo WG, et al. Rotigotine improves restless legs syndrome: a 6-month randomized, double-blind, placebo-controlled trial in the United States. Mov Disord 2010;25:1675–1683.
116. Inoue Y, Shimizu T, Hirata K, et al. Efficacy and safety of rotigotine in Japanese patients with restless legs syndrome: a phase 3, multicenter, randomized, placebo-controlled, double-blind, parallel-group study. Sleep Med 2013;14:1085–1091.
117. Benes H, Kurella B, Kummer J, Kazenwadel J, Selzer R, Kohnen R. Rapid onset of action of levodopa in restless legs syndrome: a

double-blind, randomized, multicenter, crossover trial. Sleep 1999;22:1073–1081.
118. Scholz H, Trenkwalder C, Kohnen R, Riemann D, Kriston L, Hornyak M. Levodopa for restless legs syndrome. Cochrane Database Syst Rev. 2011;(2):CD005504.
119. García-Borreguero D. Dopaminergic Augmentation in Restless Legs Syndrome/Willis-Ekbom Disease: Identification and Management. Sleep Med Clin. 2015;10(3):287-92, **xiii**.
120. Trenkwalder C, Winkelmann J, Inoue Y, Paulus W. Restless legs syndrome-current therapies and management of augmentation. Nat Rev Neurol. 2015;11(8):434-45.
121. Trenkwalder C, Allen R, Högl B, et al. Comorbidities, treatment, and pathophysiology in restless legs syndrome. Lancet Neurol. 2018;17(11):994-1005.
122. Geyer J, Bogan R. Identification and treatment of augmentation in patients with restless legs syndrome: practical recommendations. Postgrad Med. 2017;129(7):667-675.
123. Garcia-Borreguero D, Cano-Pumarega I, Garcia Malo C, Cruz Velarde JA, Granizo JJ, Wanner V. Reduced response to gabapentin enacarbil in restless legs syndrome following long-term dopaminergic treatment. Sleep Med. 2019;55:74-80.
124. Heim B, Djamshidian A, Heidbreder A, et al. Augmentation and impulsive behaviors in restless legs syndrome: Coexistence or association? Neurology. 2016;87(1):36-40.
125. Gatto EM, Aldinio V. Impulse Control Disorders in Parkinson's Disease. A Brief and Comprehensive Review. Front Neurol. 2019;10:351.
126. Winkelmann J, Allen RP, Högl B, et al. Treatment of restless legs syndrome: Evidence-based review and implications for clinical practice (Revised 2017)$_{§}$. Mov Disord. 2018;33(7):1077-1091.
127. VanMeter SA, Kavanagh ST, Warren S, Barrett RW. Dose response of Gabapentin Enacarbil versus placebo in subjects with moderate-to-severe primary restless legs syndrome: an integrated analysis of three 12-week studies. CNS Drugs. 2012;26(9):773-80.
128. Allen RP, Chen C, Garcia-Borreguero D, et al. Comparison of pregabalin with pramipexole for restless legs syndrome. N Engl J Med. 2014;370(7):621-31.
129. Trenkwalder C, Beneš H, Grote L, et al. Prolonged release oxycodone-naloxone for treatment of severe restless legs syndrome after failure of previous treatment: a double-blind, randomised, placebo-controlled trial with an open-label extension. Lancet Neurol. 2013;12(12):1141-50.
130. Marques A, Fantini ML, Morand D, et al. Emergence of restless legs syndrome after subthalamic stimulation in Parkinson's disease: a dopaminergic overstimulation? Sleep Med. 2015;16(5):583-8.
131. Klepitskaya O, Liu Y, Sharma S, Sillau SH, Tsai J, Walters AS. Deep brain stimulation improves restless legs syndrome in patients with Parkinson disease. Neurology. 2018;91(11):e1013-e1021.
132. Yoo SW, Kim JS, Oh YS, Ryu DW, Lee KS. Excessive daytime sleepiness and its impact on quality of life in de novo Parkinson's disease. Neurol Sci. 2019;40(6):1151-1156.
133. Amara AW, Chahine LM, Caspell-Garcia C, et al. Longitudinal assessment of excessive daytime sleepiness in early Parkinson's disease. J Neurol Neurosurg Psychiatry. 2017;88(8):653-662.
134. Suzuki K, Okuma Y, Uchiyama T, et al. Impact of sleep-related symptoms on clinical motor subtypes and disability in Parkinson's disease: a multicentre cross-sectional study. J Neurol Neurosurg Psychiatry. 2017;88(11):953-959.
135. Zhu K, van Hilten JJ, Marinus J. Course and risk factors for excessive daytime sleepiness in Parkinson's disease. Parkinsonism Relat Disord. 2016;24:34-40.
136. Liguori C, Mercuri NB, Albanese M, Olivola E, Stefani A, Pierantozzi M. Daytime sleepiness may be an independent symptom unrelated to sleep quality in Parkinson's disease. J Neurol. 2019;266(3):636-641.
137. Wen MC, Chan LL, Tan LCS, Tan EK. Mood and neural correlates of excessive daytime sleepiness in Parkinson's disease. Acta Neurol Scand. 2017;136(2):84-96.
138. Simuni T, Caspell-Garcia C, Coffey C, et al. Correlates of excessive daytime sleepiness in de novo Parkinson's disease: A case control study. Mov Disord. 2015;30(10):1371-81.
139. Yousaf T, Pagano G, Niccolini F, Politis M. Excessive daytime sleepiness may be associated with caudate denervation in Parkinson disease. J Neurol Sci. 2018;387:220-227.
140. Spindler M, Gooneratne NS, Siderowf A, Duda JE, Cantor C, Dahodwala N. Daytime sleepiness is associated with falls in Parkinson's disease. J Parkinsons Dis. 2013;3(3):387-91.
141. Videnovic A, Klerman EB, Wang W, Marconi A, Kuhta T, Zee PC. Timed Light Therapy for Sleep and Daytime Sleepiness Associated With Parkinson Disease: A Randomized Clinical Trial. JAMA Neurol. 2017; 74(4):411-418.
142. Postuma RB, Lang AE, Munhoz RP, et al. Caffeine for treatment of Parkinson disease: a randomized controlled trial. Neurology. 2012;79(7):651-8.
143. Högl B, Saletu M, Brandauer E, et al. Modafinil for the treatment of daytime sleepiness in Parkinson's disease: a double-blind, randomized, crossover, placebo-controlled polygraphic trial. Sleep. 2002;25(8):905-9.
144. Adler CH, Caviness JN, Hentz JG, Lind M, Tiede J. Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. Mov Disord. 2003;18(3):287-93.
145. Ondo WG, Fayle R, Atassi F, Jankovic J. Modafinail for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. J Neurol Neurosurg Psychiatry. 2005;76(12):1636-9.
146. Büchele F, Hackius M, Schreglmann SR, et al. Sodium Oxybate for Excessive Daytime Sleepiness and Sleep Disturbance in Parkinson Disease: A Randomized Clinical Trial. JAMA Neurol. 2018;75(1):114-118.
147. Suzuki K, Miyamoto M, Miyamoto T, et al. Istradefylline improves daytime sleepiness in patients with Parkinson's disease: An open-label, 3-month study. J Neurol Sci. 2017;380:230-233.
148. Rye DB. Excessive daytime sleepiness and unintended sleep in Parkinson's disease. Curr Neurol Neurosci Rep. 2006;6(2):169-76.
149. Crosta F, Desideri G, Marini C. Obstructive sleep apnea syndrome in Parkinson's disease and other parkinsonisms. Funct Neurol. 2017;32(3):137-141.
150. Zeng J, Wei M, Li T, et al. Risk of obstructive sleep apnea in Parkinson's disease: a meta-analysis. PLoS One. 2013;8(12):e82091.
151. Cochen De Cock V, Benard-Serre N, Driss V, et al. Supine sleep and obstructive sleep apnea syndrome in Parkinson's disease. Sleep Med. 2015;16(12):1497-501.
152. Huang JY, Zhang JR, Shen Y, et al. Effect of Rapid Eye Movement Sleep Behavior Disorder on Obstructive Sleep Apnea Severity and Cognition of Parkinson's Disease Patients. Chin Med J (Engl). 2018;131(8):899-906.
153. Kaminska M, Lafontaine AL, Kimoff RJ. The Interaction between Obstructive Sleep Apnea and Parkinson's Disease: Possible Mechanisms and Implications for Cognitive Function. Parkinsons Dis. 2015;2015:849472.
154. Béland SG, Postuma RB, Latreille V, et al. Observational Study of the Relation between Parkinson's Disease and Sleep Apnea. J Parkinsons Dis. 2015;5(4):805-11.
155. Harmell AL, Neikrug AB, Palmer BW, et al. Obstructive Sleep Apnea and Cognition in Parkinson's disease. Sleep Med. 2016;21:28-34.

156. Mery VP, Gros P, Lafontaine AL, Robinson A, Benedetti A, Kimoff RJ, Kaminska M. Reduced cognitive function in patients with Parkinson disease and obstructive sleep apnea. Neurology. 2017;88(12):1120-1128.
157. Neikrug AB, Liu L, Avanzino JA, et al. Continuous positive airway pressure improves sleep and daytime sleepiness in patients with Parkinson disease and sleep apnea. Sleep. 2014;37(1):177-85.
158. Terzaghi M, Spelta L, Minafra B, et al. Treating sleep apnea in Parkinson's disease with C-PAP: feasibility concerns and effects on cognition and alertness. Sleep Med. 2017;33:114-118.
159. De Pablo-Fernández E, Courtney R, Warner TT, Holton JL. A Histologic Study of the Circadian System in Parkinson Disease, Multiple System Atrophy, and Progressive Supranuclear Palsy. JAMA Neurol. 2018;75(8):1008-1012.
160. Ortuño-Lizarán I, Esquiva G, Beach TG, et al. Degeneration of human photosensitive retinal ganglion cells may explain sleep and circadian rhythms disorders in Parkinson's disease. Acta Neuropathol Commun. 2018;6(1):90.
161. Speelman AD, van de Warrenburg BP, van Nimwegen M, Petzinger GM, Munneke M, Bloem BR. How might physical activity benefit patients with Parkinson disease? Nat Rev Neurol. 2011;7(9):528-34.
162. Videnovic A, Noble C, Reid KJ, et al. Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson disease. JAMA Neurol. 2014;71(4):463-9.
163. Breen DP, Vuono R, Nawarathna U, et al. Sleep and circadian rhythm regulation in early Parkinson disease. JAMA Neurol. 2014;71(5):589-595.
164. Willis GL, Turner EJ. Primary and secondary features of Parkinson's disease improve with strategic exposure to bright light: a case series study. Chronobiol Int. 2007;24(3):521-37.