HHS Public Access

Author manuscript

Clin Geriatr Med. Author manuscript; available in PMC 2021 February 01.

Published in final edited form as:

Clin Geriatr Med. 2020 February ; 36(1): 119–130. doi:10.1016/j.cger.2019.09.005.

Overview of Sleep and Circadian Rhythm Disorders in Parkinson Disease

Priti Gros, MD[1], **Aleksandar Videnovic, MD, MSc**[2]

[1]Division of Neurology, University of Toronto, Toronto, ON, Canada

[2]Movement Disorders Unit and Division of Sleep Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

Keywords

Parkinson disease; sleep disorders; insomnia; somnolence; RLS; RBD; circadian rhythm disorders; non-motor symptoms

INTRODUCTION

Parkinson disease (PD) is the second most common neurodegenerative disease. Up to 98% of PD patients report experiencing at least one non-motor symptom (NMS)[1,2], among which sleep disorders are some of the most common. NMS are under-reported and under-recognized by PD patients, caregivers and healthcare providers[2]. Common barriers to seeking help included acceptance of symptoms, lack of awareness that a symptom is associated with PD and belief that no treatments are available[2].

In a cross-sectional survey of 358 PD patients, up to 30% of PD patients failed to report sleep disorders to their healthcare providers[2]; their prevalence can be as high as 40% in other studies[1]. Sleep disorders are associated with significant quality of life impairment[3]. Further interventions need to be put in place to encourage PD patients to report sleep disorders. Moreover, greater awareness about common sleep disorders in PD amongst healthcare providers can potentially lead to timely diagnosis and appropriate treatment.

CORRESPONDING AUTHOR: Priti Gros, MD, priti.gros@mail.utoronto.ca.
AUTHOR CONTACT INFORMATION
Priti Gros, MD, Division of Neurology, University of Toronto, St. Michael's Hospital, 30 Bond St., 3 Shuter, Office 3-040, Toronto ON, M5B 1W8
Aleksandar Videnovic, MD, MSc, Neurological Clinical Research Institute, 165 Cambridge Street, suite 600, Boston, MA 02114

DISCLOSURE STATEMENT
The authors have nothing to disclose.

CONFLICT OF INTERESTS
The authors declare that they have no conflict of interest.

In this review, we discuss common sleep problems in PD including insomnia, excessive daytime sleepiness (EDS), sleep-disordered breathing including obstructive sleep apnea (OSA), restless legs syndrome (RLS), circadian rhythm disorders and REM sleep behavior disorders (RBD).

MOST COMMON SLEEP DISORDERS ASSOCIATED WITH PARKINSON'S DISEASE

1) INSOMNIA

Definition—Insomnia is the persistent difficulty to initiate, maintain, consolidate sleep or to generate an overall good sleep quality, despite satisfying opportunity for sleep and resulting in daytime impairment[4]. PD patients report more often sleep fragmentation and early awakenings, rather than sleep initiation difficulty[5].

Epidemiology—Insomnia is thought to be the most common sleep disorder in PD, with its prevalence varying from 30-80%[6,7] With disease progression, the sleep maintenance problem increases in prevalence[6].

Pathophysiology—The elements contributing to insomnia in PD are multiple. Insomnia in PD appears to be associated with PD duration and depression[5,6]The sleep regulatory centers and circadian rhythm circuits are affected by the neurodegenerative process itself [8]. Moreover, PD patients are commonly affected by multiple symptoms such as nocturnal hypokinesia, dystonia, pain, mood changes and nocturia, which can impair sleep [9,10]. Dopaminergic agents also have an impact on sleep, although their exact effects on various PD stages, including issues of timing and dosing of these medications, remain yet to be clarified [5].

Diagnosis—A thorough sleep history, including a sleep log and the bed partner's perspective is necessary. Questionnaires can be helpful to capture night sleep disturbances, and daytime impairments[11]. Multiple questionnaires have been validated in PD, among which the PD sleep scale (PDSS) and its second version PDSS-II, the Scale for outcomes in PD (SCOPA) sleep scale have been the most commonly used [12] Polysomnography should be considered if comorbid sleep disorders are suspected.

Clinical implications—Insomnia and depression are closely related, with one often co-existing with the other[5]. PD patients with insomnia tend to have more advanced PD and is often associated with balance problems (known as postural instability) and gait difficulties, frequent wearing off of the levodopa effect, autonomic dysfunction, and hallucinations[5,13]. Another element to consider is the concomitant presence of other sleep disorders such as OSA, RBD and RLS which can contribute to sleep fragmentation and overall poor sleep. Insomnia and poor sleep quality are associated with lower health-related quality of life[14].

Management—The first step in managing insomnia in PD is to review possible contributors. PD patients should be evaluated for potential nocturnal motor symptoms. Controlled released levodopa or a dopamine agonist can be considered. One such agonist,

transdermal rotigotine patch has the advantage to provide a stable plasma level for 24 hours[15] and has been shown to help with subjective sleepiness and sleep architecture[16].

The most recent evidence-based medicine update on treatment of NMS authored by Seppi et al. concluded that eszopiclone and melatonin are "possibly useful" for treatment of insomnia in PD[18]. Non-pharmacological circadian based interventions such as light therapy are non-invasive feasible options for treatment of insomnia in PD[19].

Mood disorders should be screened and treated. Venlafaxine, tricyclic antidepressants, cognitive-behavioral therapy and even the dopamine agonist pramipexole have good evidence for their use for mood disorders in PD [18].

2) EXCESSIVE DAYTIME SLEEPINESS

Definition—Excessive daytime sleepiness (EDS) is the difficulty to remain awake and alert during the day which leads to unintended episodes of sleep or drowsiness[4]. Sleep attacks can occur in patients with EDS and are defined by unintended and inappropriate episodes of falling sleep with minimal or no prodrome of drowsiness[4].

Epidemiology—The prevalence of EDS in PD ranges from 20% to 75%[20,21]. A multi-center longitudinal study showed similar prevalence of EDS in untreated PD patients compared to healthy controls[22]; however, EDS increased in prevalence over time in PD while it remained unchanged among controls.

Pathophysiology—Multiple factors are associated with EDS in PD, such as PD stage, comorbid sleep disorders and use of dopaminergic agents. Liguori et al. suggested that EDS can occur independently of other sleep-wake disorders[23], possibly because neurodegeneration itself affect regions such as the hypothalamus and various brainstem nuclei responsible for sleep wake regulation[24]. Dopaminergic drugs have been associated with EDS and sleep attacks, dopamine agonists being the most frequent offending agents[25]. Dopaminergic drugs have possibly a dose related effect on EDS[22].

Diagnosis—Epworth Sleepiness Scale (ESS) is a commonly used screening tool. Certain electrophysiological tests are the gold standard and they include the multiple sleep latency test (MSLT) and the maintenance of wakefulness test (MWT)[26]. Comorbid sleep disorders such as RLS, OSA and RBD may influence EDS and therefore should be screened or tested with polysomnography.

Clinical implications—EDS is associated with older age, advanced PD stage, presence of postural instability and gait disturbance, autonomic dysfunction and mood disorders [20,27,28]. EDS is also associated with worse motor function, cognitive impairment and worse quality of life. Several studies revealed dissociation between the degree of daytime sleepiness and quality of nocturnal sleep; this raises a possibility for differential effects of PD-specific neurodegeneration on wake – promoting versus sleep regulatory centers.

Management—Management of EDS requires identifying possible reversible causes. Decreasing or discontinuing dopamine agonist[25] as well as treating OSA, RLS or RBD if

present can improve EDS[29,30]. Timed light therapy demonstrated a significant improvement in ESS score in a randomized placebo-controlled study[31]. Seppi et al. concluded that modafinil was “possibly useful” for treatment of EDS[18]. Caffeine is currently “investigational” as there is insufficient evidence[18]. A recent study for the use of sodium oxybate in treating EDS showed significant improvement of ESS and MSLT. However the study sample was small and long term polysomnographic monitoring is necessary to assess treatment related complications[32]. It is a controlled drug with special requirements that is best left to be managed by sleep specialists.

3) SLEEP RELATED BREATHING DISORDERS

Definition—Sleep related breathing disorders (SBD) include obstructive sleep apnea (OSA), central sleep apnea, sleep related hypoventilation and sleep related hypoxemia. In PD, OSA is the most common form of SBD and will be the focus of this section.

Epidemiology—The prevalence of OSA in PD is from 20-60% [33,34]. There is a significant variability in study methodologies including scoring system used by different sleep laboratories[35]. For example, three different standard hypopnea definitions lead to important scoring differences and therefore differences in the estimations of OSA prevalence in the general population [36] Further understanding of the mechanism of OSA in PD is necessary to better interpret potential scoring biases[35].

Pathophysiology—High BMI is typically associated with higher risk of OSA in the general population[37], but is not associated with the severity of the OSA in PD[38]. This suggests that the mechanism of OSA may be different in PD. Upper airway obstruction (UAO) in PD such as laryngopharyngeal motor dysfunction has been reported as a possible mechanism of OSA[39]. Interestingly, certain studies have reported responsiveness of OSA to levodopa[40,41].

Diagnosis—Polysomnography (PSG) or home sleep apnea testing is recommended for the diagnosis of sleep apnea in the general population[42]. In PD, home sleep apnea testing has been validated in one study with a level III portable monitoring[43]. It was found to have a reasonable specificity for moderate to severe OSA and therefore suitable to “rule in” OSA but not to “rule it out”[43].

Clinical implications—OSA is associated with excessive daytime sleepiness and cognitive dysfunction[44]. RBD is associated with less severe OSA in PD, possibly because of the increased motor activity during REM sleep[45]. PD patients with RBD and OSA have however worse cognitive dysfunction[45].

Management—Seppi et al. concluded that CPAP is “likely efficacious” and “possibly useful” in improving sleep and daytime sleepiness[18]. Prolonged continuous positive airway pressure treatment improved anxiety, cognitive function and overall sleep quality after 12 months of CPAP use[30]. An alternative to CPAP, such as carbidopa/levodopa CR (controlled release formulation) at bedtime possibly improves OSA in PD[40].

4) RESTLESS LEGS SYNDROME

Definition—Restless legs syndrome (RLS) is the urge to move the legs usually associated with leg discomfort[4]. The latter – by definition - must be caused or exacerbated by inactivity and be at least partially relieved by movement. Symptoms start or worsen in the evening or night, and cause significant discomfort[4]. RLS is closely associated with periodic limb movement of sleep (PLMs), which usually are simple stereotyped movements that can also be associated with nocturnal or diurnal disturbance[4].

Epidemiology—A meta-analysis found that the prevalence of RLS is 14% in PD, slightly higher in patients who previously received PD treatment (15%) compared to drug-naïve patients (11%)[46]. A study found that RLS is associated with an increased risk of incident PD (0.37% of PD incidence in the RLS population versus 0.13% in the controls)[47]. Lee et al. suggested that the development of RLS in PD was associated with the duration of antiparkinsonian therapy[48]. In a similar vein, other investigators have reported a lack of association between untreated PD and RLS.[49] Other studies suggest that PD patients with RLS have older age at PD onset, more advanced PD stages, severe limb parkinsonism, depression, anxiety, dysautonomia and worse nutritional status [53,54].

Pathophysiology—Ferini-Strambi et al. recently reviewed the literature around three main pathophysiological hypotheses[50]: (1) Given the common responsiveness to dopaminergic therapy, RLS and PD may share a common dopaminergic pathophysiology as well as possible genetic links[51]; (2) RLS in PD may have a different mechanism than idiopathic RLS and (3) RLS and PD may be two different diseases[50]. In other words, the interaction between RLS and PD has not been settled. In addition, there is evidence of a link between RLS and diminished iron stores in many RLS cases (with or without concomitant PD)[55,61].

Diagnosis—The criteria required to diagnose RLS are described by the third edition of International Classification of Sleep Disorders (ICSD-3)[4]. RLS has multiple mimics including non-PD conditions such as myalgia, leg cramps and arthritis. These need to be excluded by the clinician. Concomitant PD related leg symptoms such as limb stiffness and dystonia may also mimic RLS[52].

Clinical implications—RLS may be the underlying cause of insomnia, such difficulty in sleep initiation. In addition, RLS is commonly associated with periodic limb movement of sleep (PLMS) and as a consequence it can also affect sleep maintenance, can worsen sleep quality, negatively affect mood and be associated with poor quality of life.

Management—The presence of a low serum ferritin level and search for medications potentially responsible for RLS exacerbation should be assessed[55]. Evidence-based recommendations suggest dopamine agonists including pramipexole [56], rotigotine[57], ropinirole[58] as well as non-dopaminergic options such as gabapentin enacarbil[59], pregabalin[60] and IV iron[61]. However, dopamine agonists (DAs) can lead to augmentation (requirement of ever increasing doses) or worsening of symptoms after a transient period of amelioration[61]. In such cases, DAs may be suspended or transitioned to a long acting

dopaminergic or non-dopaminergic agent[62]. Subthalamic nucleus deep brain stimulation may improve RLS in PD [63,64].

5) CIRCADIAN RHYTHM DISORDERS

Circadian rhythm disorders are characterized by a chronic or recurrent sleep disturbance due to alteration of the circadian system or a misalignment between the endogenous circadian rhythm and socially determined sleep-wake schedules[4]. PD itself is influenced by the circadian rhythm. PD patients may experience diurnal fluctuations in motor and non-motor symptoms despite stable pharmacokinetics of dopaminergic medications. They may also experience seasonal fluctuations, as their disease progresses[65,66].

Mechanisms underlying these fluctuations remain unclear. Neurodegeneration affects central structures responsible for the regulation of sleep and wakefulness. PD-specific changes may affect input to the hypothalamic supraschiasmatic nucleus (SCN), the central pacemaker of the circadian system. For example, reduced exposure to ambient light and the degeneration of dopamine containing cells in the retina of PD patients, may negatively affect input to the SCN that is needed for alignment of dark/light cycles. Dopaminergic therapy has a possible bidirectional influence on the circadian rhythm [67].

Light is the main “zeitgeber” (timegiver) for the SCN, and may also have a direct alerting effect[68]. In PD, light therapy (LT) improves daytime sleepiness, sleep fragmentation, sleep quality, ease of falling sleep and mood[31]. Furthermore, some studies even suggest LT has a positive effect on motor function in PD [69].

The use of chronotherapeutics in PD including timed bright light, physical exercise and melatonin is the subject of ongoing research. These therapies have the potential to be available, inexpensive and non-invasive[70]. Further studies will be necessary to optimize PD tailored protocols[55].

6) REM SLEEP BEHAVIOR DISORDER

Definition—Rapid eye movement sleep behavior disorder (RBD) is a parasomnia described as repeated sleep-related vocalization and/or complex motor behaviors during REM sleep. Polysomnography reveals that the normal loss of muscle tone during REM sleep is lost (loss of muscle atonia)[4]. Patients often appear as “acting up their dreams” [4].

Epidemiology—A meta-analysis estimated the prevalence of RBD in PD at 23.6% and 3.4% in the general population[71]. Similarly, the DeNoPa cohort reported the prevalence of RBD as 25% in PD subjects compared to 2% in healthy controls[72]. Idiopathic RBD (iRBD) is considered a strong prodrome of synucleinopathies (PD and other related disorders). A recent large multicentre study reported a phenoconversion rate (non-PD affected individuals transitioning to PD) of 6.3% per year and 73.5% after 12 years follow-up[73]. RBD precedes onset of parkinsonism by a median time of 13 years [74], but may do so as far as 50 years in advance [75].

Pathophysiology—RBD has been related to a pontomedullary dysfunction of structures that regulate REM sleep including the locus coeruleus/subcoeruleus complex[76].

Diagnosis—Screening questionnaires are available, including the RBD Sleep Behavior Disorder Screening Questionnaire (RBDSQ)[77]. Given the prevalence of RBD mimics, polysomnography with electromyographic analysis is the gold-standard[78]. The ICSD-3 criteria include repeated observed episodes of sleep related vocalization and/or complex motor behaviors occurring during dream mentation, leading patient to report "dream enactment"[4]. There should be a clinical suspicion or electrophysiologic confirmation that these behaviors occur during REM sleep[4] or polysomnographic evidence REM sleep without atonia (RSWA)[4]. Other causes for the symptoms should be excluded such as another sleep or psychiatric disorder, substance or medication use[4].

Clinical implications—RBD, when comorbid with PD, is associated with a poorer prognosis for the latter. There is higher risk of more severe motor dysfunction, hallucinations, cognitive impairment and autonomic dysfunction [79,80]. Given its strong association with PD and related disorders, counselling selected iRBD patients (with soft neurodegenerative signs and above 50 y.o) about the potential risk of neurodegeneration may be considered [81].

Management—The most important first step in managing RBD is counselling patients and their bedpartner about bedroom safety[82]. Potential causing, or aggravating agents should be reassessed including antidepressants[83]. Mimics such as severe OSA should be screened and treated[82]. There is no level 1 efficacy data to date for the treatment of RBD in PD. Melatonin and clonazepam have both shown efficacy in several studies [84,85].

CONCLUSION

PD is associated with multiple sleep disorders, which are common and significantly impair quality of life. Routine inquiry about sleep problems from healthcare providers can increase its detection and clinical management. Sleep disorders have unique considerations in PD and have been reviewed in this article. Further research should focus on improving screening and diagnostic tools in the PD population. Mechanisms-oriented and patient centered therapeutic plans should be further developed. Level 1 efficacy data for treatment of most sleep disorders in PD are still lacking.

Acknowledgments

FUNDING

We would like acknowledge research support form NIH/NINDS. Grant number: R01NS099055.

REFERENCES

1. Chaudhuri KR, Martinez-Martin P, Schapira AH, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Mov Disord. 2006;21(7):916–923. [PubMed: 16547944]
2. 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.

3. Karlsen KH, Larsen JP, Tandberg E, Maeland JG. Influence of clinical and demographic variables on quality of life in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 1999;66(4): 431–435. [PubMed: 10201412]
4. Medicine AAoS. The International Classification of Sleep Disorders: Diagnostic and Coding Manual American Academy of Sleep Medicine. 2014;3rd ed Rev. ed. Darien IL.
5. Zhu K, van Hilten JJ, Marinus J. The course of insomnia in Parkinson's disease. Parkinsonism Relat Disord. 2016;33:51–57. [PubMed: 27639814]
6. Tholfsen LK, Larsen JP, Schulz J, Tysnes OB, Gjerstad MD. Changes in insomnia subtypes in early Parkinson disease. Neurology. 2017;88(4):352–358. [PubMed: 27986876]
7. 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. [PubMed: 28261151]
8. Diederich NJ, Vaillant M, Mancuso G, Lyen P, Tiete J. Progressive sleep 'destructuring' in Parkinson's disease. A polysomnographic study in 46 patients. Sleep Med. 2005;6(4):313–318. [PubMed: 15946897]
9. Louter M, van Sloun RJ, Pevernagie DA, et al. Subjectively impaired bed mobility in Parkinson disease affects sleep efficiency. Sleep Med. 2013;14(7):668–674. [PubMed: 23643658]
10. Gomez-Esteban JC, Zarranz JJ, Lezcano E, et al. Sleep complaints and their relation with drug treatment in patients suffering from Parkinson's disease. Mov Disord. 2006;21(7):983–988. [PubMed: 16602112]
11. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med. 2008;4(5):487–504. [PubMed: 18853708]
12. Hogl B, Arnulf I, Comella C, et al. Scales to assess sleep impairment in Parkinson's disease: critique and recommendations. Mov Disord. 2010;25(16):2704–2716. [PubMed: 20931631]
13. Chung S, Bohnen NI, Albin RL, Frey KA, Muller ML, Chervin RD. Insomnia and sleepiness in Parkinson disease: associations with symptoms and comorbidities. J Clin Sleep Med. 2013;9(11): 1131–1137. [PubMed: 24235893]
14. Shafazand S, Wallace DM, Arheart KL, et al. Insomnia, Sleep Quality, and Quality of Life in Mild to Moderate Parkinson's Disease. Ann Am Thorac Soc. 2017;14(3):412–419. [PubMed: 28231027]
15. Wang HT, Wang L, He Y, Yu G. Rotigotine transdermal patch for the treatment of neuropsychiatric symptoms in Parkinson's disease: A meta-analysis of randomized placebo-controlled trials. J Neurol Sci. 2018;393:31–38. [PubMed: 30099246]
16. 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;21:140–144. [PubMed: 27448485]
17. De Fabregues O, Ferre A, Romero O, Quintana M, Alvarez-Sabin J. Sleep Quality and Levodopa Intestinal Gel Infusion in Parkinson's Disease: A Pilot Study. Parkinsons Dis. 2018;2018:8691495. [PubMed: 30515291]
18. 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. [PubMed: 30653247]
19. Martino JK, Freelance CB, Willis GL. The effect of light exposure on insomnia and nocturnal movement in Parkinson's disease: an open label, retrospective, longitudinal study. Sleep Med. 2018;44:24–31. [PubMed: 29530365]
20. O'Suilleabhain PE, Dewey RB Jr. Contributions of dopaminergic drugs and disease severity to daytime sleepiness in Parkinson disease. Arch Neurol. 2002;59(6):986–989. [PubMed: 12056935]
21. 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. [PubMed: 28847794]
22. 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. [PubMed: 28554959]

23. 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. [PubMed: 30607535]
24. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003;24(2):197–211. [PubMed: 12498954]
25. Yeung EYH, Cavanna AE. Sleep Attacks in Patients With Parkinson's Disease on Dopaminergic Medications: A Systematic Review. Movement disorders clinical practice. 2014;1(4):307–316. [PubMed: 30363881]
26. Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the epworth sleepiness scale: failure of the MSLT as a gold standard. J Sleep Res. 2000;9(1):5–11. [PubMed: 10733683]
27. Junho BT, Kummer A, Cardoso F, Teixeira AL, Rocha NP. Clinical Predictors of Excessive Daytime Sleepiness in Patients with Parkinson's Disease. Journal of clinical neurology (Seoul, Korea). 2018;14(4):530–536.
28. Xiang YQ, Xu Q, Sun QY, et al. Clinical Features and Correlates of Excessive Daytime Sleepiness in Parkinson's Disease. Front Neurol. 2019;10:121. [PubMed: 30837940]
29. 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):177–185. [PubMed: 24470706]
30. Kaminska M, Mery VP, Lafontaine AL, et al. Change in Cognition and Other Non-Motor Symptoms With Obstructive Sleep Apnea Treatment in Parkinson Disease. J Clin Sleep Med. 2018;14(5):819–828. [PubMed: 29734988]
31. 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.
32. Buchele 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. [PubMed: 29114733]
33. Valko PO, Hauser S, Sommerauer M, Werth E, Baumann CR. Observations on sleep-disordered breathing in idiopathic Parkinson's disease. PLoS One. 2014;9(6):e100828. [PubMed: 24968233]
34. Beland 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):805–811. [PubMed: 26407040]
35. 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. [PubMed: 26509097]
36. Hirotsu C, Haba-Rubio J, Andries D, et al. Effect of Three Hypopnea Scoring Criteria on OSA Prevalence and Associated Comorbidities in the General Population. J Clin Sleep Med. 2019;15(2):183–194. [PubMed: 30736872]
37. Levy P, Kohler M, McNicholas WT, et al. Obstructive sleep apnoea syndrome. Nature reviews Disease primers. 2015;1:15015.
38. Trotti LM, Bliwise DL. No increased risk of obstructive sleep apnea in Parkinson's disease. MovDisord. 2010;25(13):2246–2249.
39. Bahia C, Pereira JS, Lopes AJ. Laryngopharyngeal motor dysfunction and obstructive sleep apnea in Parkinson's disease. Sleep Breath. 2018.
40. Gros P, Mery VP, Lafontaine AL, et al. Obstructive sleep apnea in Parkinson's disease patients: effect of Sinemet CR taken at bedtime. Sleep Breath. 2016;20(1):205–212. [PubMed: 26070532]
41. Tsai CC, Wu MN, Liou LM, Chang YP. Levodopa reverse stridor and prevent subsequent endotracheal intubation in Parkinson disease patients with bilateral vocal cord palsy: A case report. Medicine (Baltimore). 2016;95(50):e5559. [PubMed: 27977587]
42. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017;13(3):479–504. [PubMed: 28162150]

43. Gros P, Mery VP, Lafontaine AL, et al. Diagnosis of Obstructive Sleep Apnea in Parkinson's Disease Patients: Is Unattended Portable Monitoring a Suitable Tool? Parkinsons Dis. 2015;2015:258418. [PubMed: 26550519]
44. Mery VP, Gros P, Lafontaine AL, et al. Reduced cognitive function in patients with Parkinson disease and obstructive sleep apnea. Neurology. 2017;88(12): 1120–1128. [PubMed: 28228566]
45. 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. [PubMed: 29664048]
46. Yang X, Liu B, Shen H, et al. Prevalence of restless legs syndrome in Parkinson's disease: a systematic review and meta-analysis of observational studies. Sleep Med. 2018;43:40–46. [PubMed: 29482811]
47. 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;40(2).
48. 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): 579–582. [PubMed: 19097179]
49. 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):286–288. [PubMed: 21889169]
50. Ferini-Strambi L, Carli G, Casoni F, Galbiati A. Restless Legs Syndrome and Parkinson Disease: A Causal Relationship Between the Two Disorders? Front Neurol. 2018;9:551. [PubMed: 30087647]
51. Alonso-Navarro H, Garcia-Martin E, Agundez JAG, Jimenez-Jimenez FJ. Association between restless legs syndrome and other movement disorders. Neurology. 2019.
52. Hogl B, Stefani A. Restless legs syndrome and periodic leg movements in patients with movement disorders: Specific considerations. Mov Disord. 2017;32(5):669–681. [PubMed: 28186669]
53. Moccia M, Erro R, Picillo M, et al. A Four-Year Longitudinal Study on Restless Legs Syndrome in Parkinson Disease. Sleep. 2016;39(2):405–412. [PubMed: 26564123]
54. Fereshtehnejad SM, Shafieesabet M, Shahidi GA, Delbari A, Lokk J. Restless legs syndrome in patients with Parkinson's disease: a comparative study on prevalence, clinical characteristics, quality of life and nutritional status. Acta Neurol Scand.2015;131 (4):211–218. [PubMed: 25263328]
55. Videnovic A Disturbances of Sleep and Alertness in Parkinson's Disease. Curr Neurol Neurosci Rep. 2018;18(6):29. [PubMed: 29675716]
56. Ma JF, Wan Q, Hu XY, et al. Efficacy and safety of pramipexole in chinese patients with restless legs syndrome: results from a multi-center, randomized, double-blind, placebo-controlled trial. Sleep Med. 2012;13(1):58–63. [PubMed: 22137119]
57. Oertel WH, Benes H, Garcia-Borreguero D, et al. Rotigotine transdermal patch in moderate to severe idiopathic restless legs syndrome: a randomized, placebo-controlled polysomnographic study. Sleep Med. 2010;11(9):848–856. [PubMed: 20813583]
58. Walters AS, Ondo WG, Dreykluft T, Grunstein R, Lee D, Sethi K. Ropinirole is effective in the treatment of restless legs syndrome. TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. Mov Disord. 2004;19(12):1414–1423. [PubMed: 15390050]
59. Walters AS, Ondo WG, Kushida CA, et al. Gabapentin enacarbil in restless legs syndrome: a phase 2b, 2-week, randomized, double-blind, placebo-controlled trial. Clin Neuropharmacol. 2009;32(6): 311–320. [PubMed: 19667976]
60. 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): 621–631. [PubMed: 24521108]
61. Garcia-Borreguero D, Silber MH, Winkelman JW, et al. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. Sleep Med. 2016;21:1–11. [PubMed: 27448465]
62. 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. [PubMed: 27856776]

63. Chahine LM, Ahmed A, Sun Z. Effects of STN DBS for Parkinson's disease on restless legs syndrome and other sleep-related measures. Parkinsonism Relat Disord. 2011;17(3):208–211. [PubMed: 21216651]
64. 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. [PubMed: 30111549]
65. Bonuccelli U, Del Dotto P, Lucetti C, et al. Diurnal motor variations to repeated doses of levodopa in Parkinson's disease. Clin Neuropharmacol. 2000;23(1):28–33. [PubMed: 10682228]
66. Niwa F, Kuriyama N, Nakagawa M, Imanishi J. Circadian rhythm of rest activity and autonomic nervous system activity at different stages in Parkinson's disease. Auton Neurosci. 2011;165(2): 195–200. [PubMed: 21871844]
67. Bolitho SJ, Naismith SL, Rajaratnam SM, et al. Disturbances in melatonin secretion and circadian sleep-wake regulation in Parkinson disease. Sleep Med. 2014;15(3):342–347. [PubMed: 24529544]
68. Videnovic A, Messinis L. Enlightened PD: A novel treatment for Parkinson disease? Neurology. 2019;92(11):499–500. [PubMed: 30770427]
69. 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):521–537. [PubMed: 17612949]
70. Fifel K, Videnovic A. Chronotherapies for Parkinson's disease. Progress in neurobiology. 2019;174:16–27. [PubMed: 30658126]
71. Zhang J, Xu CY, Liu J. Meta-analysis on the prevalence of REM sleep behavior disorder symptoms in Parkinson's disease. BMC neurology. 2017;17(1):23. [PubMed: 28160778]
72. Mollenhauer B, Trautmann E, Sixel-Doring F, et al. Nonmotor and diagnostic findings in subjects with de novo Parkinson disease of the DeNoPa cohort. Neurology. 2013;81(14):1226–1234. [PubMed: 23997153]
73. Postuma RB, Iranzo A, Hu M, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. Brain. 2019;142(3):744–759. [PubMed: 30789229]
74. Postuma RB, Berg D. Advances in markers of prodromal Parkinson disease. Nature reviews Neurology. 2016;12(11):622–634. [PubMed: 27786242]
75. Claassen DO, Josephs KA, Ahlskog JE, Silber MH, Tippmann-Peikert M, Boeve BF. REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century. Neurology. 2010;75(6):494–499. [PubMed: 20668263]
76. Boeve BF, Silber MH, Saper CB, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain. 2007;130(Pt 11):2770–2788. [PubMed: 17412731]
77. Stiasny-Kolster K, Mayer G, Schafer S, Moller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire--a new diagnostic instrument. Mov Disord. 2007;22(16): 2386–23 93. [PubMed: 17894337]
78. Li K, Li SH, Su W, Chen HB. Diagnostic accuracy of REM sleep behaviour disorder screening questionnaire: a meta-analysis. Neurol Sci. 2017;38(6):1039–1046. [PubMed: 28314940]
79. Kim Y, Kim YE, Park EO, Shin CW, Kim HJ, Jeon B. REM sleep behavior disorder portends poor prognosis in Parkinson's disease: A systematic review. J Clin Neurosci. 2018;47:6–13. [PubMed: 29102236]
80. St Louis EK, Boeve BF. REM Sleep Behavior Disorder: Diagnosis, Clinical Implications, and Future Directions. Mayo Clin Proc. 2017;92(11):1723–1736. [PubMed: 29101940]
81. 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. [PubMed: 28082168]
82. Dauvilliers Y, Schenck CH, Postuma RB, et al. REM sleep behaviour disorder. Nature reviews Disease primers. 2018;4(1):19.

83. Gagnon JF, Postuma RB, Montplaisir J. Update on the pharmacology of REM sleep behavior disorder. Neurology. 2006;67(5):742–747. [PubMed: 16966533]

84. 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. [PubMed: 20191945]

85. McCarter SJ, Boswell CL, St Louis EK, et al. Treatment outcomes in REM sleep behavior disorder. Sleep Med. 2013;14(3):237–242. [PubMed: 23352028]

KEY POINTS

- Sleep disorders are among the most common non-motor symptoms of Parkinson's disease, can occur at any stage of the disease and significantly affect quality of life.
- This article aims to provide an overview of different sleep disorders affecting PD patients including insomnia, excessive daytime sleepiness, sleep-disordered breathing, restless legs syndrome, circadian rhythms disorders and REM sleep behavior disorders.
- Non-pharmacological and pharmacological treatment options are used in the management of disorders of sleep in PD
- Further research on the pathophysiology and treatment of sleep dysfunction associated with PD is needed.

SYNOPSIS

Sleep disorders are common among PD patients and significantly affect quality of life. They are often under-recognized and under-treated. Improved awareness of common sleep problems in PD among healthcare providers is necessary. Mechanisms of sleep disorders in PD remain poorly understood. Tailored treatment and evidence for efficacy are lacking. The purpose of this review is to provide an overview and update on the most common sleep disorders in PD. We review specific features of the most common sleep disorders in PD, including insomnia, excessive daytime sleepiness, sleep-disordered breathing, restless legs syndrome, circadian rhythm disorders and REM sleep behavior disorders. For each disorder, an overview and update on the definition, epidemiology, pathophysiology, diagnosis, clinical features and treatment are presented. Areas of further research interests are discussed.