Management Recommendations on Sleep Disturbance of Patients with Parkinson's Disease

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Key words: Excessive Daytime Sleepiness; Insomnia; Parkinson's Disease; Rapid Eye Movement Sleep Behavior Disorder; Sleep Disturbance

Introduction

Sleep disturbance is one of the most common nonmotor symptoms in Parkinson's disease (PD). Sleep disturbance affects 40–98% of PD patients in the world.[1-3] In China, the prevalence of PD patients with sleep disturbance ranges from 47.66% to 89.10%.[4-9] Sleep disturbance usually has adverse impact on the quality of life of PD patients. A possible pathogenesis of PD with sleep disturbance include thalamocortical pathway degeneration and changes of neurotransmitter systems.[3] The etiology of sleep disturbance is multifactorial, involving degeneration of areas regulating sleep, sleep structure affected by drugs, sleep disturbance induced by drug, and sleep fragmentation by multiple factors.[3] Although three reviews on the sleep disturbances of PD have recently been published, there is no consensus of recommendations on the management of PD patients with sleep disturbance.[1,3,10]

This consensus aims to provide recommendations for PD patients with sleep disturbances based on the current available evidence and expert opinions.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.247210

Literature Search, Articles Review, and Consensus Meetings

A consensus committee, including neurologists in PD from China and the United Kingdom, was established to review the literature on the sleep disturbance of PD. The committee members aligned their opinions with controversial clinical

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Received: 21-08-2018 **Edited by:** Yuan-Yuan Ji
How to cite this article: Liu CF, Wang T, Zhan SQ, Geng DQ, Wang J, Liu J, Shang HF, Wang LJ, Chan P, Chen HB, Chen SD, Wang YP, Zhao ZX, Chaudhuri KR. Management Recommendations on Sleep Disturbance of Patients with Parkinson's Disease. Chin Med J 2018;131:2976-85.

questions using the current evidence and clinical experience in two face-to-face meetings followed by electronic communication.

Literature search was conducted in PubMed between January 2000 and August 2017 using keywords including "Parkinson's disease," "parkinsonism," "sleep disturbance," "sleep disorder," "insomnia," "excessive daytime sleepiness," "obstructive sleep apnea," "REM sleep behavior disorder," "RBD," "restless legs syndrome," "RLS," "nocturia," "sleep-related movement disorders," "parasomnias," "sleep-disordered breathing," "SBD," "diurnal," "deep brain stimulation," and "sleep attack."

Two consensus meetings were separately held in Suzhou (August 27, 2017) and Zhuhai (December 2, 2017) of China. Based on the predetermined criteria, the quality of each article was evaluated, which was consistent with the method of previous published articles.[11,12] The efficacy of each drug was defined as "efficacious," "likely efficacious," "unlikely efficacious," "nonefficacious," and "insufficient evidence." Implications of each treatment for clinical practice were also defined as "clinically useful," "possibly useful," "investigational," "unlikely useful," and "not useful." Safety of each treatment was defined as "acceptable risk without specialized monitoring," "acceptable risk with specialized monitoring," "unacceptable risk," and "insufficient evidence to make conclusions on the safety of the intervention."

Based on the *International Classification of Sleep Disorders (the third edition)*[13] and clinical experience, five types of sleep disturbance in PD were selected for this consensus including insomnia, excessive daytime sleepiness (EDS), rapid eye movement (REM) sleep behavior disorder (RBD), restless legs syndrome (RLS), and sleep-disordered breathing (SDB).

Insomnia

The prevalence of insomnia in PD is 27–80%.[10] In China, this prevalence is 30.0–86.8%.[9,14-20]

Key factors related with insomnia of PD patients include female gender, disease duration of PD, depression, anxiety, and others, which may lead to sleep fragmentation. Main causes related to sleep fragmentation include night motor dysfunction and nocturia.[3] Some drugs (e.g., selegiline) may increase the risk of insomnia.[10]

PD patients usually have impairment in the upper brainstem and low midbrain, which is a key to the sleep–wake regulation. In addition, PD may have an impact on arousal system.[21] Insomnia in PD patients can be diagnosed utilizing clinical history, questionnaires, polysomnography (PSG), and actigraphy.[3]

If insomnia in PD is neither iatrogenic nor due to motor complications of PD, cognitive behavioral therapy including suggestions for sleep–wake behavior hygiene, stimulus control therapy, sleep restriction, relaxation, as well as cognitive techniques should be considered.[10] Music therapy may be another option for the treatment of insomnia in PD patients.[22]

A double-blind controlled study found that single dose of levodopa/carbidopa (Sinemet CR) could not significantly improve total sleep time, sleep latency, and sleep fragmentation of PD patients[23] (quality score, 62.5%). Another randomized placebo-controlled study demonstrated that administration of Sinemet CR could not significantly improve the objective sleep parameters of PD patients including sleep latency, total sleep time, and awakening times[24] (quality score, 75%). Based on the evidence, Sinemet CR is deemed nonefficacious in improving insomnia in patients with PD.

A randomized, placebo-controlled study showed that ropinirole could increase the PD sleep scale (PDSS) score of PD patients, suggesting that it can improve the sleep quality of PD patients[25] (quality score, 90%). Another double-blind, placebo-controlled study found that ropinirole could increase the PDSS score of PD patients[26] (quality score, 90%). Based on the results of these studies, ropinirole is considered efficacious in improving insomnia in patients with PD.

A randomized, placebo-controlled study found that transdermal rotigotine patch could significantly increase the PDSS score of patients with advanced PD[27] (quality score, 90%). Further five studies (2 randomized controlled trials [RCTs] and 3 open studies) demonstrated that rotigotine could significantly improve the PDSS-2, sleep efficiency, sleep fragmentation, and sleep quality of PD patients[28-32] (quality score, 93% for RECOVER study and 85% for Pierantozzi *et al*.). Based on the results of these studies, rotigotine patch is considered efficacious in improving insomnia in patients with PD.

A randomized, placebo-controlled study found that pramipexole could significantly increase the PDSS score of patients with advanced PD[27] (quality score, 90%). Based on the results of the study, pramipexole is considered efficacious in improving insomnia in patients with PD. Insomnia is also listed as a side effect of dopamine agonists.

A single-center prospective observational study found that compared to monotherapy with LD, the combination of rasagiline and LD significantly decreased the sleep latency and elongated sleep time of PD patients[33] (quality score, 61%). A double-blind, baseline-controlled study found that rasagiline may be beneficial to the sleep quality of PD patients with sleep disturbance.[34] Based on the result of the study, rasagiline is likely efficacious in improving insomnia in patients with PD.

A RCT found that eszopiclone could significantly decrease wakeness and improve sleep quality of PD patients[35] (quality score, 95%). Based on the result of the study, eszopiclone is efficacious in improving insomnia in patients with PD.

A randomized preliminary study found that doxepin could improve the insomnia symptoms of PD patients, although only six PD patients were included in this study[36] (quality score,

68%). Based on the result of the study, doxepin is likely efficacious in improving insomnia in patients with PD.

Two RCTs demonstrated that melatonin could prolong the sleep duration and improve the sleep quality of PD patients[37,38] (quality score, 76% for Dowling and 75% for Medeiros). Based on the results of these studies, melatonin is efficacious in improving insomnia in patients with PD.

An open study found that quetiapine was effective and safe in patients with PD.[39] Based on the result of this study, there is insufficient evidence for the efficacy of quetiapine in improving insomnia in PD patients.

In addition, one RCT found that the respective incidence of insomnia with respect to the use of placebo, ropinirole, and rotigotine was similar in the treatment of early PD patients (5%, 6%, and 6%, respectively).[40]

However, 17 studies were included in the management of insomnia in PD patients [Table 1].

Recommendations

- Before treatment, both the cause and the subtype of insomnia in PD patients need to be carefully evaluated. PD patients with insomnia should be treated based on definite etiology (e.g., akinesia and drugs). If the insomnia is related to nocturnal motor symptoms, dopaminergic therapy (dopamine agonists [e.g., rotigotine transdermal patch], long-acting LDs [Sinemet], and monoamine oxidase B inhibitors) should be optimized initially (expert opinion)
- Cognitive-behavioral therapy is the preferred option in PD patients with insomnia regardless of etiology (Level A recommendation by the American Academy of Sleep Medicine)
- Dopamine agonists (e.g., rotigotine, pramipexole, and ropinirole), eszopiclone, and melatonin followed by rasagiline and doxepin may be considered for the management of insomnia in patients with PD (evidence based)
- The pharmacological treatment of the insomnia in PD patients includes the treatment of insomnia itself and secondary insomnia in the context of PD progression. The treatment of insomnia in PD patients refers to the drugs for single insomnia approved by the Food and Drug Administration. If the insomnia of PD patients still cannot improve after optimization treatment for nocturnal motor symptoms, traditional drugs for treating insomnia could be considered. Antidepressants and anxiolytic drugs may also improve the insomnia of PD patients (expert opinion).

Table 1: Conclusions on the management of insomnia in PD patients

Drugs	Treatment of insomnia
Levodopa–carbidopa	
Efficacy	Nonefficacious
Safety	Insufficient evidence to make conclusions on the safety of the intervention
Practice implications	Not useful
Ropinirole	
Efficacy	Efficacious
Safety	Acceptable risk without specialized monitoring
Practice implications	Clinically useful
Pramipexole	
Efficacy	Efficacious
Safety	Acceptable risk without specialized monitoring
Practice implications	Clinically useful
Rotigotine	
Efficacy	Efficacious
Safety	Acceptable risk without specialized monitoring
Practice implications	Clinically useful
Rasagiline	
Efficacy	Likely efficacious
Safety	Insufficient evidence to make conclusions on the safety of the intervention
Practice implications	Possibly useful
Eszopiclone	
Efficacy	Efficacious
Safety	Acceptable risk without specialized monitoring
Practice implications	Clinically useful
Doxepin	
Efficacy	Likely efficacious
Safety	Insufficient evidence to make conclusions on the safety of the intervention
Practice implications	Possibly useful
Melatonin	
Efficacy	Efficacious
Safety	Acceptable risk without specialized monitoring
Practice implications	Clinically useful
Quetiapine	
Efficacy	Insufficient evidence
Safety	Insufficient evidence to make conclusions on the safety of the intervention
Practice implications	Investigational

PD: Parkinson's disease.

Excessive Daytime Sleepiness

The prevalence of EDS in patients with PD is 21–76%.[3,10] In China, this prevalence is 13.2–46.9%.[4,5,17,41-43] In patients with early PD, the prevalence of EDS could increase from 11.8% at baseline to 23.4% after 5 years. The prevalence of EDS can be influenced by male gender, older age, nontremor subtype, autonomic dysfunction, cognitive impairment, depression and anxiety, disease severity, and duration.[44,45]

EDS can be caused by advanced age, PD-related change of sleep–wake cycle, periodic limb movements, daytime immobility, and dopaminergic drugs. Early PD patients with more severe daytime sleepiness would be at higher risk to develop EDS.[10]

The etiology of EDS in PD includes change of sleep–wake regulation, side effect of dopamine agonist treatment, poor

sleep quality at night, genetic factors, male gender, disease duration, disease stage, hypocretin level, benzodiazepines, autonomic dysfunction, and depression.[3] The EDS in patients with PD can be diagnosed by clinical history, scales (Epworth Sleepiness Scale [ESS] and Inappropriate Sleep Composite Score), actigraphy, PSG, and the Multiple Sleep Latency Test/Maintenance of Wakefulness Test.

It is critical to inform PD patients with EDS to concern sleep hygiene.[10] Other nonpharmacological treatments include cognitive-behavioral therapy, light treatment, repetitive transcranial magnetic stimulation, and deep brain stimulation.

Three studies (2 RCTs and 1 open study) demonstrated that modafinil could significantly improve the EDS of PD patients.[46-48] However, another RCT found that modafinil could not improve the EDS of PD patients.[49] Meta-analysis of the three trials showed a significant reduction of 2.24 points of ESS in PD patients after the treatment with modafinil.[50] In the statement of the treatments for the nonmotor symptoms of PD from the Movement Disorder Society in 2011, the evidence of modafinil for treating EDS of PD is insufficient.[51] Based on the results of these studies, there is insufficient evidence for the efficacy of modafinil in treating EDS of PD patients. The adverse events related to modafinil include insomnia, which is mild, and can be alleviated with the decrease of dosage.[10]

A randomized controlled study demonstrated that caffeine consumption resulted in a nonsignificant reduction of ESS in PD patients.[52] Another randomized controlled study revealed that there was a slight improvement in EDS of PD patients with the treatment of caffeine over the first 6 months, which attenuated over time.[53] Based on the results of these studies, there is insufficient evidence for the efficacy of caffeine in treating EDS of PD patients.

An open study found that the ESS scores of PD patients significantly decreased after they were treated with istradefylline for 2 and 3 months.[54] Based on the results of the study, there is insufficient evidence for the efficacy of istradefylline in EDS of PD patients.

An open study demonstrated that methylphenidate decreased the ESS of PD patients.[55] However, the sample size was low, and there were no other large-scale, double-blind, placebo-controlled trials. There is insufficient evidence for the efficacy of methylphenidate in EDS of PD patients.

A randomized, double-blind, placebo-controlled study found that atomoxetine was well tolerated and significantly improved daytime sleepiness in PD patients[56] (quality score, 88%). Based on the study, atomoxetine is efficacious in improving the EDS of PD patients.

An open-label study found that sodium oxybate significantly improved the ESS of PD patients.[57] Based on the study, there is insufficient evidence for the efficacy of sodium oxybate in treating the EDS of PD patients.

Dopamine agonists may increase the incidence of EDS in PD patients.[58,59] A RCT found that the respective incidence of EDS in PD patients with placebo, rotigotine, and ropinirole was 6%, 8%, and 14%, while the incidence of sleep attacks in PD patients was 0, 2%, and 3%, respectively.[40] A comparative study found that EDS was identified in PD patients treated with cabergoline, pramipexole, and LD.[60]

A double-blind randomized trial found that pitolisant was efficacious in improving the EDS of patients with narcolepsy compared with placebo and was well tolerated when compared with modafinil.[61]

Altogether, 15 studies were included in the management of EDS in PD patients [Table 2].

Recommendations

- In PD patients with EDS, it must be elicited from history whether EDS is associated with drugs, surgery, nocturnal sleep, or secondary to other sleep disorders (expert opinion)
- If EDS is associated with treatment, the dose of the relevant drugs should be reduced or stopped; relevant drugs include hypnotics with antihistamine activity, benzodiazepines, and other antidepressants with sedative action. There should be regulation of the timing and dosage in dopaminergic administration. The combination of selegiline and levodopa might decrease EDS (expert opinion)
- Atomoxetine could be considered for the treatment of EDS in PD patients with depression if available. Modafinil, adenosine receptor antagonists (i.e., caffeine and istradefylline), sodium oxybate, methylphenidate, and pitolisant may improve the EDS of PD patients, but this needs to be validated in randomized controlled double-blind studies with a larger sample size (evidence based)
- Cognitive-behavioral therapy, light treatment, repetitive transcranial magnetic stimulation, and deep brain stimulation might improve the EDS of PD patients (expert opinion).

Rapid Eye Movement Sleep Behavior Disorder

The prevalence of RBD in patients with PD is 19–70%.[3,10,62,63] In China, this prevalence is 22.2–60.0%.[4,9,17,43,64-71] The conversion rate from RBD to neurodegenerative diseases is 35.0–98.8%. The conversion rate from RBD to PD is 18.6–65.0%.[72-76]

In PD, RBD typically occurs preceding that of motor symptoms. The association between PD and RBD can be explained as neurodegeneration in certain brainstem structures at Braak stage 1–2.[10] The pathogenesis of RBD in PD includes degeneration of laterodorsal tegmental nuclei, which is associated with the inhibition of locomotor generators in REM sleep, as well as magnocellular reticular formation, pedunculopontine nucleus, pontine reticular formation, and decreased numbers of nigrostriatal dopamine

Table 2: Conclusions on the management of EDS in PD patients

Drugs	Treatment of EDS
Modafinil	
Efficacy	Insufficient evidence
Safety	Acceptable risk without specialized monitoring
Practice implications	Investigational
Caffeine	
Efficacy	Insufficient evidence
Safety	Insufficient evidence to make conclusions on the safety of the intervention
Practice implications	Investigational
Istradefylline	
Efficacy	Insufficient evidence
Safety	Insufficient evidence to make conclusions on the safety of the intervention
Practice implications	Investigational
Methylphenidate	
Efficacy	Insufficient evidence
Safety	Insufficient evidence to make conclusions on the safety of the intervention
Practice implications	Investigational
Atomoxetine	
Efficacy	Efficacious
Safety	Acceptable risk without specialized monitoring
Practice implications	Clinically useful
Sodium oxybate	
Efficacy	Insufficient evidence
Safety	Insufficient evidence to make conclusions on the safety of the intervention
Practice implications	Investigational
Rotigotine	
Efficacy	Insufficient evidence
Safety	Insufficient evidence to make conclusions on the safety of the intervention
Practice implications	Investigational
Ropinirole	
Efficacy	Insufficient evidence
Safety	Insufficient evidence to make conclusions on the safety of the intervention
Practice implications	Investigational
Pramipexole	
Efficacy	Insufficient evidence
Safety	Insufficient evidence to make conclusions on the safety of the intervention
Practice implications	Investigational

PD: Parkinson's disease; EDS: Excessive daytime sleepiness.

transporters.[3] RBD in PD can be diagnosed by video-PSG, RBD-SQ, and RBD-SS.

The nonpharmacological treatment of PD patients with RBD includes ensuring the safety of the patient and bed partner and the security of the bedroom.[10] Auditory pure-tone stimulation might be another option for treating the RBD of PD patients, especially for secondary RBD.[77]

One double-blind randomized, controlled study found that melatonin may significantly improve the sleep quality of PD patients, which can be considered either as monotherapy or adjunct therapy of PD patients with RBD[38] (quality score, 75%). Based on the results of the study, melatonin is efficacious in improving RBD in patients with PD.

An open prospective study found that rotigotine may partially improve RBD-related symptoms of PD patients in China.[78] However, there is still insufficient evidence for the efficacy of rotigotine in treating RBD of PD patients.

A prospective study found that pramipexole cannot improve the RBD-related symptoms of patients with PD.[79] However, in another study by Sasai *et al*.,[80] although pramipexole is not better than clonazepam in treating idiopathic RBD, it was apparently effective in patients with RBD having a lower RWA/REM ratio, which indicates lower severity of the disorder. Hence, it can be considered in mild cases.[80,81] Overall, however, there is insufficient evidence for the efficacy of pramipexole in the treatment of RBD in PD patients.

Drugs which are related with worsening of RBD caused by acute administration include selective serotonin reuptake inhibitors and the other ones. Drugs which are related with aggravation of RBD caused by withdrawal include ethanol, benzodiazepines, barbiturates, meprobamate, and pentazocine.[75] These agents should either be stopped if possible, reduced, or changed to alternative medications less likely to aggravate RBD whenever feasible.

Altogether, three studies were included in the management of RBD in PD patients [Table 3].

Recommendations

- Some agents which could worsen or induce RBD should be either stopped if possible, reduced, or changed to alternative medications less likely to aggravate RBD whenever feasible (expert opinion)
- In PD patients with RBD who have injurious behavior or potential injurious behavior, establishment of a safe sleep environment is a preferred option (expert opinion)
- Melatonin should be considered as preferred option for the treatment of RBD in PD patients. Dopamine agonists (i.e., rotigotine transdermal patch and pramipexole) may be effective in the management of RBD in PD patients, which might be considered as the treatment of RBD in PD patients (evidence based)
- Clonazepam is the most efficacious drug in the treatment of idiopathic RBD, which has not been validated in PD patients with RBD. As clonazepam increases the risk of falls in PD patients, it can be considered as alternative option once other drugs are not effective (expert opinion).

Restless Legs Syndrome

Fifteen percent of PD patients have RLS.[10] In China, this prevalence ranged from 8.41% to 34.85%.[4,5,17] The variability of RLS of PD patients in different studies may be associated with mimic phenomena and other factors (e.g., dystonia).[82]

FP-CIT SPECT study found that more dopamine transporters were preserved at the head of caudate in PD patients with RLS, indicating that there might be a nonlinear association between dopaminergic dysfunction and RLS.[10,83] In addition, iron deficiency and poor nutrition status may be associated with the RLS of PD patients.[84] RLS in PD could be diagnosed by video-PSG.

In PD patients with mild RLS, lifestyle adjustment is recommended. Other nonpharmacological treatments include rubbing or massaging the affected limbs, bathing in hot or cold water, physical activity, and distraction therapy.[10]

In PD patients with RLS, serum level of ferritin should be measured. If the serum level of ferritin is <50–75 μg/ml or transferrin saturation is <20%, oral iron supplementation is recommended. If oral iron is not tolerated or is contraindicated, intravenous iron can be considered.[10] Drugs which may aggravate RLS, including antidopaminergic drugs, antihistamines, and antidepressants, should be stopped if possible.[10]

Five studies (1 RCT and 4 open studies) demonstrated that rotigotine may improve the RLS-related symptoms in PD patients[28,31,85-87] (quality score, 93% for RECOVER study). Based on the results of these studies, rotigotine is efficacious in improving RLS in patients with PD.

A meta-analysis found that gabapentin, enacarbil, pregabalin, and rotigotine were the most effective options for RLS among dopaminergic drugs (pramipexole, ropinirole, and rotigotine) and α-2-δ ligands (gabapentin, enacarbil, and pregabalin).[88] A Cochrane Database systematic review found that the effectiveness of benzodiazepines in RLS is currently unknown.[89] However, the sample populations in the meta-analysis and systematic review above are RLS patients without PD.

Altogether, five studies, one meta-analysis, and one Cochrane Database systematic review were included in the management of RLS in PD patients [Table 4].

Recommendations

- The treatment aim of RLS is applying safe and effective therapies including both pharmacologic and nonpharmacologic approaches, to relieve RLS symptoms and improve quality of life
- Concomitant medications that may induce or aggravate RLS symptoms (e.g., antidopaminergic drugs) should be stopped whenever possible. In PD patients with RLS, other secondary factors and contributing comorbidities should be excluded such as metabolic disorders, end-stage renal disease, diabetes, pregnancy, and serotonergic antidepressants. Treating the iron deficiency should be the first-line of treatment (expert opinion)
- In PD patients with mild RLS, lifestyle adjustment is recommended. To prevent augmentation, the lowest possible effective dose of dopaminergic agents is recommended and long-acting DAs are preferred (expert opinion)
- Dopamine agonist (i.e., rotigotine patch) is strongly recommended in the management of RLS in PD patients (evidence based)
- α2δ calcium channel ligands may be considered in the treatment of RLS in PD patients, possibly with less risk of augmentation which need to be validated in PD patients with RLS (expert opinion).

Table 3: Conclusions on the management of RBD in PD patients

Drugs	Treatment of RBD
Melatonin	
Efficacy	Efficacious
Safety	Acceptable risk without specialized monitoring
Practice implications	Clinically useful
Rotigotine	
Efficacy	Insufficient evidence
Safety	Insufficient evidence to make conclusions on the safety of the intervention
Practice implications	Investigational
Pramipexole	
Efficacy	Insufficient evidence
Safety	Insufficient evidence to make conclusions on the safety of the intervention
Practice implications	Investigational

REM: Rapid eye movement; PD: Parkinson's disease; RBD: REM sleep behavior disorder.

Table 4: Conclusions on the management of RLS in PD patients

Drugs	Treatment of RLS
Rotigotine	
Efficacy	Efficacious
Safety	Acceptable risk without specialized monitoring
Practice implications	Clinically useful
Pramipexole	
Efficacy	Insufficient evidence
Safety	Insufficient evidence to make conclusions on the safety of the intervention
Practice implications	Investigational
Ropinirole	
Efficacy	Insufficient evidence
Safety	Insufficient evidence to make conclusions on the safety of the intervention
Practice implications	Investigational
Pregabalin	
Efficacy	Insufficient evidence
Safety	Insufficient evidence to make conclusions on the safety of the intervention
Practice implications	Investigational
Gabapentin	
Efficacy	Insufficient evidence
Safety	Insufficient evidence to make conclusions on the safety of the intervention
Practice implications	Investigational

PD: Parkinson's disease; RLS: Restless legs syndrome.

Sleep-Disordered Breathing

Single OSA is rare in patients with PD. The prevalence of OSA in PD patients is 20–60%.[10] PD itself may be involved in the pathogenesis of OSA. The involuntary motor symptoms of PD patients may influence the muscle structure of the upper airways, thus leading to the presence of abnormal vital capacity consistent with the obstruction of the upper airway system. PD is associated with the dysfunction of the autonomic nerve system, which possibly has an impact on respiratory control. In addition, insomnia and sleep fragmentation may induce respiratory disorders.[90] Recent studies found that OSA was associated with the somnolence and cognitive disorders of PD patients.[91,92] The pathogenesis of OSA in PD patients may be associated with the extension of degenerative disease into the brain stem, thus leading to the impairment of the function of the respiratory center. In addition, a study indicated that dopamine agonists may increase the risk of OSA in PD patients.[93]

OSA patients typically have symptoms such as frequent snoring with sudden awakening and sleep apnea. PSG is the gold standard for the diagnosis of OSA.

Continuous positive airway pressure (CPAP) is the gold standard treatment option of OSA. Other nonpharmacological treatment options include weight control, sleeping on one side, BiPAP, ASV, and oxygen therapy.[10] In order to alleviate the difficulty of turning around at night, appropriately increasing the dose of dopaminergic drugs may be helpful.[94] Mandibular advancement device is expected to be one tool of treatment of OSA in patients with PD.[95]

A multinational, double-blind, RCT demonstrated that transdermal rotigotine patch may significantly improve 10 individual Modified PDSS-2 items including respiratory problems and snoring of PD patients.[28] A secondary study found that bedtime Sinemet CR may reduce OSA in PD patients.[96]

Recommendations

- The treatment goal of PD patients with SDB is to decrease the incidence and alleviate symptoms of SDB, thus decreasing EDS, as well as improve the cognitive dysfunction and emotional disorders induced by SDB (expert opinion)
- The general treatment of PD patients with SDB includes losing weight, control of diet and weight, appropriate exercise, cessation or reduced alcohol and smoking, careful use of sedative-hypnotic drugs and the other drugs inducing or aggravating SDB (e.g., clonazepam), sleeping on one side, raising the bed head, and avoiding overwork at daytime (expert opinion)
- CPAP is the first treatment option of PD patients with SDB (expert opinion).

In conclusion, the recommendations of this consensus are both based on the current available evidence and expert opinions. Since the evidence of drugs in the treatment of PD patients with sleep disturbance is limited, more and more large-sample randomized trials with high quality, as well as real-world studies on the diagnosis, evaluation, new technologies, and new treatment options are warranted to be conducted in these groups of patients, thus helping the decision-making of neurologists in the future.

Acknowledgment

The authors appreciate UCB Pharma China for facilitating the two consensus meetings. The authors also appreciate Dr. Yi-Min Wan for providing editorial support of this manuscript as well as Dr. Yun Shen for collecting materials for this manuscript.

Financial support and sponsorship

This project was supported by grants from the National Key R and D Program of China (No. 2017YFC0909100) and the Jiangsu Provincial Special Program of Medical Science and Jiangsu Provincial Key R&D Program (No. BE2018658).

Conflicts of interest

There are no conflicts of interest.

References

1. Amara AW, Chahine LM, Videnovic A. Treatment of sleep dysfunction in Parkinson's disease. Curr Treat Options Neurol 2017;19:26. doi: 10.1007/s11940-017-0461-6.
2. Albers JA, Chand P, Anch AM. Multifactorial sleep disturbance in Parkinson's disease. Sleep Med 2017;35:41-8. doi: 10.1016/j.sleep.2017.03.026.
3. Falup-Pecurariu C, Diaconu Ş. Sleep dysfunction in Parkinson's disease. Int Rev Neurobiol 2017;133:719-42. doi: 10.1016/bs.irn.2017.05.033.
4. Lou F, Cao D, Luo XG, Ren Y. Clinical characteristics of sleep disorders in different subtypes of patients with Parkinson disease (in Chinese). Chin J Clin 2011;5:5567-72.
5. Yu SY, Liu Z, Sun L, Huang XY, Cao CJ, Zuo LJ, *et al*. Relevant factors of sleep disorders and their influences on the quality in patients with Parkinson disease (in Chinese). Chin J Clin 2012;6:3956-63.
6. Ma HL, Ren Y. Correlation analysis of sleep disorder and cognitive dysfunction in patients with Parkinson disease (in Chinese). Chin J Clin 2015;9:4309-15.
7. Zhang H, Gu Z, An J, Wang C, Chan P. Non-motor symptoms in treated and untreated Chinese patients with early Parkinson's disease. Tohoku J Exp Med 2014;232:129-36. doi: 10.1620/tjem.232.129.
8. Wang Y, Yang YC, Wu HJ, Zhao ZX. Sleeping characteristics of PD patients and its influencing factors (in Chinese). Chin J Geriatr Heart Brain Vessel Dis 2016;18:722-5.
9. Huang J, Zhuo W, Zhang Y, Sun H, Chen H, Zhu P, *et al.* Cognitive function characteristics of Parkinson's disease with sleep disorders. Parkinsons Dis 2017;2017:4267353. doi: 10.1155/2017/4267353.
10. Loddo G, Calandra-Buonaura G, Sambati L, Giannini G, Cecere A, Cortelli P, *et al.* The treatment of sleep disorders in Parkinson's disease: From research to clinical practice. Front Neurol 2017;8:42. doi: 10.3389/fneur.2017.00042.
11. Fox SH, Katzenschlager R, Lim SY, Ravina B, Seppi K, Coelho M, *et al.* The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the motor symptoms of Parkinson's disease. Mov Disord 2011;26 Suppl 3:S2-41. doi: 10.1002/mds.23829.
12. Goetz CG, Koller WC, Poewe W. Management of Parkinson's disease: An evidence-based review. Mov Disord 2002;17:S1-66. doi: 10.1002/mds.5555.
13. American Academy of Sleep Medicine. International Classification of Sleep Disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
14. He YH, Zhu YH, Liu L, Wang P. Clinical analysis of dyssomnia in Parkinson patients (in Chinese). Chin J Pract Nerv Dis 2008;11:29-30.

15. Li L, Liu ZG, Gan J, Zhou MZ, Zhou ZY. Analysis of sleep disorders in Parkinson disease patients at early stage (in Chinese). Chin J Contemp Neurol Neurosurg 2008;8:176-80.
16. Gao JH, Yan YF, Sun L, Liu Z, Huang XY, Zhang W. Non-motor symptoms in patients with Parkinson's disease (in Chinese). Chin Gen Pract 2010;13:2576-9.
17. Ma XR, Sun ZK, Liu YR, Zhang B. Analysis of occurrence rate of non-motor symptoms in 126 patients in Parkinson's disease (in Chinese). Chin J Pract Nerv Dis 2013;16:3-5.
18. Tian ZY. Analysis of characteristics of Parkinson's disease clinical sleep disorders (in Chinese). Chin J Med Guide 2014;16:623-6.
19. Liang PY, Cui LQ, Wu ZH, Yu JL, Chen MZ. A survey of sleep related cognitions in patients with Parkinson's disease and related nursing (in Chinese). Clin Med Eng 2015;22:928-9.
20. Zhang H, Zhang Y, Lu ZN, Dong HJ, Luo C, Huang TT. Influence of sleep disorders on health-related quality of life in patients with Parkinson's disease (in Chinese). Chin J Neuroimmunol Neurol 2017;24:21-4.
21. Park M, Comella CL. Insomnia in Parkinson's disease. In: Videnovic A, Högl B, editors. Disorders of Sleep and Circadian Rhythmsin Parkinson's Disease. Vienna: Springer; 2015. p. 79-91.
22. Jespersen KV, Koenig J, Jennum P, Vuust P. Music for insomnia in adults. Cochrane Database Syst Rev 2015;8:CD010459. doi: 10.1002/14651858.CD010459.pub2.
23. Stocchi F, Barbato L, Nordera G, Berardelli A, Ruggieri S. Sleep disorders in Parkinson's disease. J Neurol 1998;245 Suppl 1:S15-8.
24. 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;18:590-6. doi: 10.1111/j.1468-1331.2010.03213.x.
25. Ray Chaudhuri K, Martinez-Martin P, Rolfe KA, Cooper J, Rockett CB, Giorgi L, *et al.* Improvements in nocturnal symptoms with ropinirole prolonged release in patients with advanced Parkinson's disease. Eur J Neurol 2012;19:105-13. doi: 10.1111/j.1468-1331.2011.03442.x.
26. Pahwa R, Stacy MA, Factor SA, Lyons KE, Stocchi F, Hersh BP, *et al.* Ropinirole 24-hour prolonged release: Randomized, controlled study in advanced Parkinson disease. Neurology 2007;68:1108-15. doi: 10.1212/01.wnl.0000258660.74391.c1.
27. Poewe WH, Rascol O, Quinn N, Tolosa E, Oertel WH, Martignoni E, *et al.* Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: A double-blind, double-dummy, randomised controlled trial. Lancet Neurol 2007;6:513-20. doi: 10.1016/S1474-4422(07)70108-4.
28. Trenkwalder C, Kies B, Rudzinska M, Fine J, Nikl J, Honczarenko K, *et al.* Rotigotine effects on early morning motor function and sleep in Parkinson's disease: A double-blind, randomized, placebo-controlled study (RECOVER). Mov Disord 2011;26:90-9. doi: 10.1002/mds.23441.
29. Calandra-Buonaura G, Guaraldi P, Doria A, Zanigni S, Nassetti S, Favoni V, *et al.* Rotigotine objectively improves sleep in Parkinson's disease: An open-label pilot study with actigraphic recording. Parkinsons Dis 2016;2016:3724148. doi: 10.1155/2016/3724148.
30. Pierantozzi M, Placidi F, Liguori C, Albanese M, Imbriani P, Marciani MG, *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. doi: 10.1016/j.sleep.2016.01.016.
31. Pagonabarraga J, Piñol G, Cardozo A, Sanz P, Puente V, Otermín P, *et al.* Transdermal rotigotine improves sleep fragmentation in Parkinson's disease: Results of the multicenter, prospective SLEEP-FRAM study. Parkinsons Dis 2015;2015:131508. doi: 10.1155/2015/131508.
32. Giladi N, Fichtner A, Poewe W, Boroojerdi B. Rotigotine transdermal system for control of early morning motor impairment and sleep disturbances in patients with Parkinson's disease. J Neural Transm (Vienna) 2010;117:1395-9. doi: 10.1007/s00702-010-0506-4.
33. Schettino C, Dato C, Capaldo G, Sampaolo S, Di Iorio G, Melone MA, *et al.* Rasagiline for sleep disorders in patients with Parkinson's disease: A prospective observational study. Neuropsychiatr Dis Treat 2016;12:2497-502. doi: 10.2147/NDT.S116476.
34. Schrempf W, Fauser M, Wienecke M, Brown S, Maaß A, Ossig C, *et al.* Rasagiline improves polysomnographic sleep parameters in patients with Parkinson's disease: A double-blind, baseline-controlled trial. Eur J Neurol 2018;25:672-9. doi: 10.1111/ene.13567.
35. Menza M, Dobkin RD, Marin H, Gara M, Bienfait K, Dicke A, *et al.* Treatment of insomnia in Parkinson's disease: A controlled trial of eszopiclone and placebo. Mov Disord 2010;25:1708-14. doi: 10.1002/mds.23168.
36. Rios Romenets S, Creti L, Fichten C, Bailes S, Libman E, Pelletier A, *et al.* Doxepin and cognitive behavioural therapy for insomnia in patients with Parkinson's disease – A randomized study. Parkinsonism Relat Disord 2013;19:670-5. doi: 10.1016/j.parkreldis.2013.03.003.
37. Dowling GA, Mastick J, Colling E, Carter JH, Singer CM, Aminoff MJ, *et al.* Melatonin for sleep disturbances in Parkinson's disease. Sleep Med 2005;6:459-66. doi: 10.1016/j.sleep.2005.04.004.
38. Medeiros CA, Carvalhedo de Bruin PF, Lopes LA, Magalhães MC, de Lourdes Seabra M, de Bruin VM, *et al.* Effect of exogenous melatonin on sleep and motor dysfunction in Parkinson's disease. A randomized, double blind, placebo-controlled study. J Neurol 2007;254:459-64. doi: 10.1007/s00415-006-0390-x.
39. Juri C, Chaná P, Tapia J, Kunstmann C, Parrao T. Quetiapine for insomnia in Parkinson disease: Results from an open-label trial. Clin Neuropharmacol 2005;28:185-7. doi: 10.1097/01.wnf.0000174932.82134.e2.
40. Giladi N, Boroojerdi B, Korczyn AD, Burn DJ, Clarke CE, Schapira AH, *et al.* Rotigotine transdermal patch in early PARKINSON'S disease: A randomized, double-blind, controlled study versus placebo and ropinirole. Mov Disord 2007;22:2398-404. doi: 10.1002/mds.21741.
41. He JG, Wang LN, Zhang X, Wang ZF, Zhang BH, Zhang XH, *et al*. Clinical characteristics of sleep disorders in 96 patients in Parkinson's disease (in Chinese). Chin J Geriatr 2005;24:831-4.
42. Lou F, Li M, Ren Y. Analysis of excessive daytime sleepiness of patients with Parkinson disease at early stage (in Chinese). Chin J Clin 2012;6:5907-11.
43. Gong Y, Xiong KP, Mao CJ, Shen Y, Hu WD, Huang JY, *et al.* Clinical manifestations of Parkinson disease and the onset of rapid eye movement sleep behavior disorder. Sleep Med 2014;15:647-53. doi: 10.1016/j.sleep.2013.12.021.
44. Amara AW, Chahine LM, Caspell-Garcia C, Long JD, Coffey C, Högl B, *et al.* Longitudinal assessment of excessive daytime sleepiness in early Parkinson's disease. J Neurol Neurosurg Psychiatry 2017;88:653-62. doi: 10.1136/jnnp-2016-315023.
45. 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. doi: 10.1016/j.parkreldis.2016.01.020.
46. Adler CH, Caviness JN, Hentz JG, Lind M, Tiede J. Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson'sParkinson's disease. Mov Disord 2003;18:287-93. doi: 10.1002/mds.10390.
47. Högl B, Saletu M, Brandauer E, Glatzl S, Frauscher B, Seppi K, *et al.* Modafinil for the treatment of daytime sleepiness in Parkinson's disease: A double-blind, randomized, crossover, placebo-controlled polygraphic trial. Sleep 2002;25:905-9.
48. Nieves AV, Lang AE. Treatment of excessive daytime sleepiness in patients with Parkinson's disease with modafinil. Clin Neuropharmacol 2002;25:111-4.
49. Ondo WG, Fayle R, Atassi F, Jankovic J. Modafinil for daytime somnolence in Parkinson's disease: Double blind, placebo controlled parallel trial. J Neurol Neurosurg Psychiatry 2005;76:1636-9. doi: 10.1136/jnnp.2005.065870.
50. Rodrigues TM, Castro Caldas A, Ferreira JJ. Pharmacological interventions for daytime sleepiness and sleep disorders in Parkinson's disease: Systematic review and meta-analysis. Parkinsonism Relat Disord 2016;27:25-34. doi: 10.1016/j.parkreldis.2016.03.002.
51. Seppi K, Weintraub D, Coelho M, Perez-Lloret S, Fox SH, Katzenschlager R, *et al.* The movement disorder society evidence-based medicine review update: Treatments for the non-motor symptoms of Parkinson's disease. Mov Disord 2011;26 Suppl 3:S42-80. doi: 10.1002/mds.23884.
52. Postuma RB, Lang AE, Munhoz RP, Charland K, Pelletier A,

Moscovich M, *et al.* Caffeine for treatment of Parkinson disease: A randomized controlled trial. Neurology 2012;79:651-8. doi: 10.1212/WNL.0b013e318263570d.
53. Postuma RB, Anang J, Pelletier A, Joseph L, Moscovich M, Grimes D, *et al.* Caffeine as symptomatic treatment for Parkinson disease (Café-PD): A randomized trial. Neurology 2017;89:1795-803. doi: 10.1212/WNL.0000000000004568.
54. Suzuki K, Miyamoto M, Miyamoto T, Uchiyama T, Watanabe Y, Suzuki S, *et al.* Istradefylline improves daytime sleepiness in patients with Parkinson's disease: An open-label, 3-month study. J Neurol Sci 2017;380:230-3. doi: 10.1016/j.jns.2017.07.045.
55. Devos D, Krystkowiak P, Clement F, Dujardin K, Cottencin O, Waucquier N, *et al.* Improvement of gait by chronic, high doses of methylphenidate in patients with advanced Parkinson's disease. J Neurol Neurosurg Psychiatry 2007;78:470-5. doi: 10.1136/jnnp.2006.100016.
56. Weintraub D, Mavandadi S, Mamikonyan E, Siderowf AD, Duda JE, Hurtig HI, *et al.* Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease. Neurology 2010;75:448-55. doi: 10.1212/WNL.0b013e3181ebdd79.
57. Ondo WG, Perkins T, Swick T, Hull KL Jr. Jimenez JE, Garris TS, *et al.* Sodium oxybate for excessive daytime sleepiness in Parkinson disease: An open-label polysomnographic study. Arch Neurol 2008;65:1337-40. doi: 10.1001/archneur.65.10.1337.
58. Elmer LW, Surmann E, Boroojerdi B, Jankovic J. Long-term safety and tolerability of rotigotine transdermal system in patients with early-stage idiopathic Parkinson's disease: A prospective, open-label extension study. Parkinsonism Relat Disord 2012;18:488-93. doi: 10.1016/j.parkreldis.2012.01.008.
59. LeWitt PA, Boroojerdi B, Surmann E, Poewe W, SP716 Study Group, SP715 Study Group. *et al.* Rotigotine transdermal system for long-term treatment of patients with advanced Parkinson's disease: Results of two open-label extension studies, CLEOPATRA-PD and PREFER. J Neural Transm (Vienna) 2013;120:1069-81. doi: 10.1007/s00702-012-0925-5.
60. Pal S, Bhattacharya KF, Agapito C, Chaudhuri KR. A study of excessive daytime sleepiness and its clinical significance in three groups of Parkinson's disease patients taking pramipexole, cabergoline and levodopa mono and combination therapy. J Neural Transm (Vienna) 2001;108:71-7. doi: 10.1007/s007020170098.
61. Dauvilliers Y, Bassetti C, Lammers GJ, Arnulf I, Mayer G, Rodenbeck A, *et al.* Pitolisant versus placebo or modafinil in patients with narcolepsy: A double-blind, randomised trial. Lancet Neurol 2013;12:1068-75. doi: 10.1016/S1474-4422(13)70225-4.
62. Zhang J, Xu CY, Liu J. Meta-analysis on the prevalence of REM sleep behavior disorder symptoms in Parkinson's disease. BMC Neurol 2017;17:23. doi: 10.1186/s12883-017-0795-4.
63. 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;38:163-70. doi: 10.1007/s10072-016-2744-1.
64. Li D, Huang P, Zang Y, Lou Y, Cen Z, Gu Q, *et al.* Abnormal baseline brain activity in Parkinson's disease with and without REM sleep behavior disorder: A resting-state functional MRI study. J Magn Reson Imaging 2017;46:697-703. doi: 10.1002/jmri.25571.
65. Sun Q, Wang T, Jiang TF, Huang P, Li DH, Wang Y, *et al.* Effect of a leucine-rich repeat kinase 2 variant on motor and non-motor symptoms in Chinese Parkinson's disease patients. Aging Dis 2016;7:230-6. doi: 10.14336/AD.2015.1026.
66. Chen W, Kang WY, Chen S, Wang Y, Xiao Q, Wang G, *et al.* Hyposmia correlates with SNCA variant and non-motor symptoms in Chinese patients with Parkinson's disease. Parkinsonism Relat Disord 2015;21:610-4. doi: 10.1016/j.parkreldis.2015.03.021.
67. Hu Y, Yu SY, Zuo LJ, Piao YS, Cao CJ, Wang F, *et al.* Investigation on abnormal iron metabolism and related inflammation in Parkinson disease patients with probable RBD. PLoS One 2015;10:e0138997. doi: 10.1371/journal.pone.0138997.
68. Hu Y, Yu SY, Zuo LJ, Cao CJ, Wang F, Chen ZJ, *et al.* Parkinson disease with REM sleep behavior disorder: Features, α-synuclein, and inflammation. Neurology 2015;84:888-94. doi: 10.1212/WNL.0000000000001308.
69. Yang ZJ, Wei J, Mao CJ, Zhang JR, Chen J, Ji XY, *et al.* Retinal nerve fiber layer thinning: A window into rapid eye movement sleep behavior disorders in Parkinson's disease. Sleep Breath 2016;20:1285-92. doi: 10.1007/s11325-016-1366-4.
70. Wang Y, Shen Y, Xiong KP, He PC, Mao CJ, Li J, *et al.* Tonic electromyogram density in multiple system atrophy with predominant parkinsonism and Parkinson's disease. Chin Med J 2017;130:684-90. doi: 10.4103/0366-6999.201603.
71. Shen Y, Xiong KP, Li J, Mao CJ, Chen J, He PC, *et al.* Clinical correlates of rapid eye movement sleep without atonia in Parkinson's disease. Clin Neurophysiol 2015;126:1198-203. doi: 10.1016/j.clinph.2014.09.014.
72. Iranzo A, Molinuevo JL, Santamaría J, Serradell M, Martí MJ, Valldeoriola F, *et al.* Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: A descriptive study. Lancet Neurol 2006;5:572-7. doi: 10.1016/S1474-4422(06)70476-8.
73. Iranzo A, Tolosa E, Gelpi E, Molinuevo JL, Valldeoriola F, Serradell M, *et al.* Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: An observational cohort study. Lancet Neurol 2013;12:443-53. doi: 10.1016/S1474-4422(13)70056-5.
74. Gagnon JF, Postuma RB, Mazza S, Doyon J, Montplaisir J. Rapid-eye-movement sleep behaviour disorder and neurodegenerative diseases. Lancet Neurol 2006;5:424-32. doi: 10.1016/S1474-4422(06)70441-0.
75. St Louis EK, Boeve AR, Boeve BF. REM sleep behavior disorder in Parkinson's disease and other synucleinopathies. Mov Disord 2017;32:645-58. doi: 10.1002/mds.27018.
76. Boeve BF, Silber MH, Ferman TJ, Lin SC, Benarroch EE, Schmeichel AM, *et al.* Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. Sleep Med 2013;14:754-62. doi: 10.1016/j.sleep.2012.10.015.
77. Zhang L, Xu Y, Zhuang J, Peng H, Wu H, Zhao Z, *et al.* Effect of low-intensity pure tone auditory stimulation on patients with rapid eye movement sleep behavior disorder. Neurol Res 2016;38:792-8. doi: 10.1080/01616412.2016.1204495.
78. Wang Y, Yang Y, Wu H, Lan D, Chen Y, Zhao Z, *et al.* Effects of rotigotine on REM sleep behavior disorder in Parkinson disease. J Clin Sleep Med 2016;12:1403-9. doi: 10.5664/jcsm.6200.
79. Kumru H, Iranzo A, Carrasco E, Valldeoriola F, Marti MJ, Santamaria J, *et al.* Lack of effects of pramipexole on REM sleep behavior disorder in Parkinson disease. Sleep 2008;31:1418-21.
80. Sasai T, Matsuura M, Inoue Y. Factors associated with the effect of pramipexole on symptoms of idiopathic REM sleep behavior disorder. Parkinsonism Relat Disord 2013;19:153-7. doi: 10.1016/j.parkreldis.2012.08.010.
81. Tan SM, Wan YM. Pramipexole in the treatment of REM sleep behaviour disorder: A critical review. Psychiatry Res 2016;243:365-72. doi: 10.1016/j.psychres.2016.06.055.
82. Högl B, Stefani A. Restless legs syndrome and periodic leg movements in patients with movement disorders: Specific considerations. Mov Disord 2017;32:669-81. doi: 10.1002/mds.26929.
83. Moccia M, Erro R, Picillo M, Santangelo G, Spina E, Allocca R, *et al.* A four-year longitudinal study on restless legs syndrome in Parkinson disease. Sleep 2016;39:405-12. doi: 10.5665/sleep.5452.
84. Fereshtehnejad SM, Shafieesabet M, Shahidi GA, Delbari A, Lökk 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;131:211-8. doi: 10.1111/ane.12307.
85. Kim JM, Chung SJ, Kim JW, Jeon BS, Singh P, Thierfelder S, *et al.* Rotigotine transdermal system as add-on to oral dopamine agonist in advanced Parkinson's disease: An open-label study. BMC Neurol 2015;15:17. doi: 10.1186/s12883-015-0267-7.
86. Vallderiola F, Compta Y, Aparicio J, Tarradellas J, Salazar G, Oliver JM, *et al.* Effects of night-time use of rotigotine on nocturnal symptoms in Parkinson's disease. Parkinsons Dis 2015;2015:475630. doi: 10.1155/2015/475630.
87. Wang Y, Yang YC, Lan DM, Wu H, Zhao ZX. An observational clinical and video-polysomnographic study of the effects of

rotigotine in sleep disorder in Parkinson's disease. Sleep Breath 2017;21:319-25. doi: 10.1007/s11325-016-1414-0.
88. Iftikhar IH, Alghothani L, Trotti LM. Gabapentin enacarbil, pregabalin and rotigotine are equally effective in restless legs syndrome: A comparative meta-analysis. Eur J Neurol 2017;24:1446-56. doi: 10.1111/ene.13449.
89. Carlos K, Prado GF, Teixeira CD, Conti C, de Oliveira MM, Prado LB, *et al.* Benzodiazepines for restless legs syndrome. Cochrane Database Syst Rev 2017;3:CD006939. doi: 10.1002/14651858.CD006939.pub2.
90. 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. doi: 10.1155/2015/849472.
91. Mery VP, Gros P, Lafontaine AL, Robinson A, Benedetti A, Kimoff RJ, *et al.* Reduced cognitive function in patients with Parkinson disease and obstructive sleep apnea. Neurology 2017;88:1120-8. doi: 10.1212/WNL.0000000000003738.
92. Harmell AL, Neikrug AB, Palmer BW, Avanzino JA, Liu L, Maglione JE, *et al.* Obstructive sleep apnea and cognition in Parkinson's disease. Sleep Med 2016;21:28-34. doi: 10.1016/j.sleep.2016.01.001.
93. Valko PO, Hauser S, Sommerauer M, Werth E, Baumann CR. Observations on sleep-disordered breathing in idiopathic Parkinson's disease. PLoS One 2014;9:e100828. doi: 10.1371/journal.pone.0100828.
94. Cochen De Cock V, Benard-Serre N, Driss V, Granier M, Charif M, Carlander B, *et al.* Supine sleep and obstructive sleep apnea syndrome in Parkinson's disease. Sleep Med 2015;16:1497-501. doi: 10.1016/j.sleep.2014.09.014.
95. Phillips CL, Grunstein RR, Darendeliler MA, Mihailidou AS, Srinivasan VK, Yee BJ, *et al.* Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: A randomized controlled trial. Am J Respir Crit Care Med 2013;187:879-87. doi: 10.1164/rccm.201212-2223OC.
96. Gros P, Mery VP, Lafontaine AL, Robinson A, Benedetti A, Kimoff RJ, *et al.* Obstructive sleep apnea in Parkinson's disease patients: Effect of Sinemet CR taken at bedtime. Sleep Breath 2016;20:205-12. doi: 10.1007/s11325-015-1208-9.