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. In China, the prevalence of PD patients with sleep disturbance ranges from 47.66% to 89.10%. 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. 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. 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.

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

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
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.[1] 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.[1]

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,
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 (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. 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).

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).

### Excessive Daytime Sleepiness

The prevalence of EDS in patients with PD is 21–76%. In China, this prevalence is 13.2–46.9%. 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.

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.

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

| Table 1: Conclusions on the management of insomnia in PD patients |
|------------------------|--------------------------|
| Drugs | Treatment of Insomnia |
| Levodopa–carbidopa | Nonefficacious |
| Efficacy | Insufficient evidence to make conclusions on the safety of the intervention |
| Safety | Practice implications |
| Practice implications | Not useful |
| Rasagiline | Likely efficacious |
| Efficacy | Insufficient evidence to make conclusions on the safety of the intervention |
| Safety | Practice implications |
| Practice implications | Possibly useful |
| Eszopiclone | Clinically useful |
| Efficacy | Acceptable risk without specialized monitoring |
| Safety | Practice implications |
| Practice implications | Clinically useful |
| Doxepin | Efficacious |
| Efficacy | Acceptable risk without specialized monitoring |
| Safety | Practice implications |
| Practice implications | Clinically useful |
| Quetiapine | Efficacious |
| Efficacy | Insufficient evidence |
| Safety | Practice implications |
| Practice implications | Investigational |

PD: Parkinson’s disease.
sleep quality at night, genetic factors, male gender, disease duration, disease stage, hypocretin level, benzodiazepines, autonomic dysfunction, and depression.\[^{53}\] 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.\[^{60}\] 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 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%.\[^{6,8,9,17,43,64‑71}\] 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        | Insufficient evidence                                                            |
| Efficacy         | Acceptable risk without specialized monitoring                                   |
| Practice implications | Investigational                  |
| Caffeine         | Insufficient evidence                                                            |
| Efficacy         | Insufficient evidence to make conclusions on the safety of the intervention     |
| Practice implications | Investigational                  |
| Istradefylline   | Insufficient evidence                                                            |
| Efficacy         | Insufficient evidence to make conclusions on the safety of the intervention     |
| Practice implications | Investigational                  |
| Methylphenidate  | Insufficient evidence                                                            |
| Efficacy         | Insufficient evidence to make conclusions on the safety of the intervention     |
| Practice implications | Investigational                  |
| Atomoxetine      | Efficacious                                                                      |
| Efficacy         | Acceptable risk without specialized monitoring                                   |
| Practice implications | Clinically useful                 |
| Sodium oxybate   | Insufficient evidence                                                            |
| Efficacy         | Insufficient evidence to make conclusions on the safety of the intervention     |
| Practice implications | Investigational                  |
| Rotigotine       | Insufficient evidence                                                            |
| Efficacy         | Insufficient evidence to make conclusions on the safety of the intervention     |
| Practice implications | Investigational                  |
| Pramipexole      | Insufficient evidence                                                            |
| Efficacy         | Insufficient evidence to make conclusions on the safety of the intervention     |
| Practice implications | Investigational                  |

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

transporters. 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.[80,81] Auditory pure-tone stimulation might be another option for treating RBD in PD patients, especially for secondary RBD.[82]

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.[79] 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).[38]
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. In addition, iron deficiency and poor nutrition status may be associated with the RLS of PD patients. 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.

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. Drugs which may aggravate RLS, including antidiopaminergic drugs, antihistamines, and antidepressants, should be stopped if possible.

Five studies (1 RCT and 4 open studies) demonstrated that rotigotine may improve the RLS-related symptoms in PD patients (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). A Cochrane Database systematic review found that the effectiveness of benzodiazepines in RLS is currently unknown. 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].

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

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

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

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

**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., antidiopaminergic 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).
The treatment of sleep disorders in Parkinson’s disease (PD) 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.

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Conflicts of interest
There are no conflicts of interest.

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