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REVIEW ARTICLE

Pharmacological and Non-pharmacological Treatments of Sleep Disorders in Parkinson's Disease

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Abstract: Sleep disorders are one of the most common non-motor symptoms in Parkinson's disease (PD). It can cause a notable decrease in quality of life and functioning in PD patients, as well as place a huge burden on both patients and caregivers. The most cited sleep disorders in PD included insomnia, restless legs syndrome (RLS), rapid eye movement (REM), sleep behavior disorders (RBD), excessive daytime sleepiness (EDS) and sleep disordered breathing (SDB), which can appear alone or several at the same time. In this review, we listed the recommended pharmacological treatments for common sleep disorders in PD, and discussed the recommended dosages, benefits and side effects of relative drugs. We also discussed non-pharmacological treatments to improve sleep quality, including sleep hygiene education, exercise, deep brain stimulation, cognitive behavior therapy and complementary therapies. We tried to find proper interventions for different types of sleep disorders in PD, while minimizing relative side effects.

Keywords: Parkinson's disease, insomnia, restless legs syndrome, RBD, excessive daytime sleepiness, sleep disordered breathing, pharmacological treatments, non-pharmacological treatments.

1. INTRODUCTION

Sleep disorders, as one of the most common non-motor symptoms in Parkinson's disease (PD), can occur at any stage in PD and place a huge burden on both patients and caregivers [1]. It is reported that 60%-98% PD patients experience sleep disturbances, and up to 60% even suffer from sleep disturbances long before any obvious motor symptom appears [2]. Despite the high prevalence, only less than half of sleep problems are reported to doctors and receive enough attention [3]. Sleep disorders are related to decreased cognitive function, increased risk of falls and worsen quality of life (QOL) [4, 5]. It will not only increase motor dysfunction but also increase the non-motor symptom burden [6]. In addition to health risks, sleep disorders can also bring significant socio-economic consequences. Patients and society must bear higher healthcare costs and other indirect costs, such as loss of labor market income [7].

Sleep disorders have increasingly been considered as an inherent component of the degenerative process itself, associated with neuronal degeneration and both α-synuclein and tau deposition in key structures involved in sleep cycle and maintenance, such as the locus coeruleus, raphe nuclei, paramammilary and posterior hypothalamic nuclei, amygdala, and thalamus [8]. In humans, the level of arousal and alternations of sleep-wake cycle is controlled by the hypothalamus and a number of brainstem nuclei. [8]. Specifically, the major wakefulness-promoting areas, including the hypothalamus, the pedunculopontine nucleus (PPN), the locus coeruleus and the raphe nuclei; and the major sleep-promoting nucleus is the ventrolateral preoptic nucleus of the anterior hypothalamus [9, 10]. Dopaminergic system plays an important role in the sleep-wake cycle. Dopamine (DA) in the basal ganglia (BG) promotes sleep *via* D2 receptors, while the extra-BG dopaminergic system promotes wakefulness *via* D1 and D2 receptors [11]. At the same time, in animal models, researchers found that the release of DA increased in the dark period and decreased in the light period, which indicating DA activity might have circadian rhythm [12]. The pathology of PD is characterized by degeneration of DA neurons in the pars compacta of substantia nigra (SN), which results in a marked DA depletion in the striatum [13]. DA neurons in SN innervate not only the striatum but also other BG nuclei, including globus pallidus and subthalamic nucleus [14]. When DA neurons in SN are degenerated to a certain degree, which leads to a significant depletion of DA in BG and extra-BG dopaminergic system, the sleep-wake cycle of PD patients will be disrupted and various types of sleep disorders appear [13].

Most cited sleep disorders in PD include insomnia, restless legs syndrome (RLS), rapid eye movement (REM), sleep behavior disorders (RBD), excessive daytime sleepiness (EDS) and sleep disordered breathing (SDB) [15, 16].

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They may occur one or more at a time and sometimes share the same treatment. Common methods for detecting sleep disorders in PD include detailed medical history, questionnaires about sleep quality, and polysomnography. Recommend questionnaires include but are not limited to Parkinson's Disease Sleep Scale (PDSS), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and Stanford sleepiness scale (SSS) [17].

Management of sleep disorders in PD should start with sleep hygiene education and effective non-pharmacological treatments. Pharmacological management usually begins with optimization of antiparkinsonian therapy, especially alternations of dopaminergic drugs. Then according to different types of sleep disorders, specialized and personalized drugs are given. Although many drugs have proved to have certain therapeutic effects on sleep disorders, the overall treatment effects in PD population are still far from satisfactory with effect discrepancy and various side effects. Thus, it is of vital importance to choose the right treatments and drug dosage for different types of sleep disorders.

This review discussed common sleep disorders in PD patients and listed pharmacological and non-pharmacological interventions to alleviate them and improve sleep quality. We listed the recommended pharmacological treatments for common sleep disorders in PD, and discussed the recommended dosages, benefits and side effects of related drugs. We tried to find a proper way to select personalized pharmacological and non-pharmacological interventions for different types of sleep disorders in PD, while improving patients' tolerance and minimize side effects.

2. SLEEP DISORDERS AND PHARMACOLOGICAL TREATMENTS

2.1. Insomnia

Insomnia is the most common sleep disorder in PD. It can happen in 30% to 80% PD patients and sometimes exists long before obvious motor dysfunction appears [18]. Patients with insomnia can seldom initiate, maintain, and consolidate sleep or often fail to keep a good sleep quality overnight despite satisfying environment [15]. The most common insomnia subtype in PD is sleep maintenance obstacle, which is also called sleep fragmentation [19]. Studies have demonstrated that chronic sleep fragmentation can cause cognitive impairment in PD patients, especially impairments in executive functions, including deficits in attention, phonemic verbal fluency, and working memory [19, 20].

Insomnia in PD is a result of the mixture of factors. It can be partly explained by overnight PD motor symptoms, non-motor symptoms like nocturia and nocturnal pain, depression, effect of antiparkinsonian medications, autonomic dysfunction, and comorbid sleep-wake regulatory disorders [21, 18]. Nighttime PD motor and non-motor symptoms can be improved by antiparkinsonian medications, but these medications can reversely cause or exacerbate insomnia. DA agonists (*e.g.* ropinirole, rotigotine, pramipexole, cabergoline and pergolide), selegiline, rasagiline and entacapone are all reported to have a risk to induce or exacerbate insomnia [22-29]. Other drugs associated with insomnia include selective serotonin reuptake inhibitors (*e.g.* fluvoxamine, sertraline, and fluoxetine), the acetylcholinesterase inhibitors (*e.g.* galantamine, donepezil, and rivastigmine), and the serotonin–norepinephrine reuptake inhibitor (venlafaxine) [30]. But the paradox is that some of these drugs can also be used to treat insomnia or other types of sleep disorders, which makes it difficult to adjust patients' medication plans. Clinically, PD patients with higher Unified Parkinson's Disease Rating Scale (UPDRS) scores, longer disease duration, female, depression, anxiety and motor fluctuations are more likely to experience insomnia [31]. And some studies reveal that patients with insomnia will experience less time in REM, but whether that means less chance to develop RBD still need further research [32].

The first step to manage insomnia in PD is to evaluate whether antiparkinsonian medicines need adjustment (Table **1**). Although DA preparations like carbidopa–levodopa controlled release can improve nocturnal akinesia, there is not enough evidence on improving subjective and objective sleep quality [33]. DA agonist can significantly improve PD patients' subjective and objective sleep quality. Studies have demonstrated that DA agonists can improve both motor and non-motor PD symptoms and permit a reduction in adjunctive levodopa dose, making it a choice to manage insomnia [34]. But it can also cause daytime somnolence and sudden sleep attack [30]. Different types of DA agonists also show different effects. Specifically, sustained-release preparations improved subjective sleep quality more than immediate-release preparations, without a significant increase in side effects. Rotigotine showed similar sleep-improving effects as pramipexole immediate release, but it is preferred more to individuals with motor fluctuations and insomnia at the same time [30, 35]. Also, DA agonists are demonstrated to have a dose-dependent effect; that is, higher doses induce wakefulness during sleep while lower doses reduce wakefulness and improve sleep quality [36]. This phenomenon is mainly related to the biphasic effects of D2 receptors, such that low doses reduce waking and increase slow wave sleep (SWS) and REM, whereas large doses induce opposite effects [36, 37]. There are also some reports that show continuous levodopa-carbidopa intestinal gel (LCIG) infusion that improves sleep quality in advanced PD patients [38]. Sustained LCIG treatment is recommended for advanced PD patients when conventional levodopa based oral or transdermal therapy is ineffective, and it can lead to significant improvements in motor fluctuations, non-motor symptoms, mood disorders, cognition impairment and gastrointestinal disorders. However, most of the relevant experiments are only performed in patients with advanced PD and the operation requirements are high, so it is still too early to make large-scale clinical applications.

Doxepin and quetiapine are atypical sedative antipsychotics frequently used to treat hallucinations and psychotic symptoms in PD [39]. It is believed that sedating antipsychotics cannot only treat mood disorders but also other comorbidities such as nighttime pain, which contributes to sleep quality improvement [40]. Doxepin and quetiapine are well tolerated in most PD patients, especially in those with dementia and impaired cognitive function, but they may also cause or aggravate other types of sleep disorders [41, 42].

Table 1. Pharmacological treatments of insomnia in PD patients.

-	Recommended Dose	Benefits	Side Effects
Dopaminergic agonists			
Rotigotine	2-16mg [47]	improve subjective sleep quality; improve overnight and early morning motor performance; reduce nocturia	local site reactions; dyskinesias; headache; dizziness; daytime somnolence; fatigue; nausea
Pramipexole immediate release	0.375- 4.5 mg [48]	improve subjective sleep quality; improve overnight motor and non-motor symptoms	visual hallucinations; daytime somnolence; sudden sleep attack; fatigue; nausea; ICD; orthostatic hypotension; edema
Pramipexole sustained release	0.375- 4.5 mg [48]	improve subjective sleep quality; improve overnight motor and non-motor symptoms	visual hallucinations; daytime somnolence; sudden sleep attack; fatigue; nausea; ICD; orthostatic hypotension; edema
Ropinirole	0.75-15 mg [49]	improve subjective sleep quality; improve overnight motor and non-motor symptoms	dyskinesias; headache; dizziness; daytime somnolence; sudden sleep attack; nausea; leg edema
Ropinirole prolonged release	2-24mg [34]	improve subjective sleep quality; improve overnight motor and non-motor symptoms	dyskinesia; hallucinations; daytime somnolence; dizziness; nausea; orthostatic hypotension; leg edema
Cabergoline	4–6 mg [50]	improve subjective sleep quality; increase sleep efficiency and SWS	hallucinations; dizziness; daytime somnolence; nausea; cardiopulmonary fibrosis
Sedative antipsychotics			
Doxepin	10 mg [51]	improve subjective sleep quality; reduce fatigue; improved scores of MoCA;	transient orthostatic; dizziness; fatigue; nausea
Quetiapine	12.5-50 mg [39]	improve subjective sleep quality; reduce hallucinations	worsen PD motor symptoms; aggravate RLS; daytime somnolence; nausea
Non-benzodiazepines			
Eszoplicone	2-3 mg [52]	improve subjective sleep quality; reduce number of awakenings after sleep onset	daytime somnolence; dizziness
Melatonin and melatonin agonists			
Melatonin	3-5mg [44, 53]	improve subjective sleep quality	mild headaches; daytime somnolence; fatigue
Melatonin sustained release	2mg [54, 55]	improve subjective sleep quality; reduce nocturia	mild headaches; daytime somnolence; fatigue
Agomelatine	12.5–50 mg [45]	improve subjective sleep quality; improve depressive symptoms	headache; dizziness; fatigue; nausea
Others			
Zonisamide	25-50 mg [46]	improve subjective sleep quality; improve PD motor symptoms; improve depressive symptoms	aggravate insomnia; increased blood creatine phosphokinase; decreased appetite; constipation
Levodopa-carbidopa intestinal gel	1 dose [38] (containing 20 mg/ml levodopa and 5 mg/ml carbidopa)	improve subjective sleep quality; improve PD motor symptoms; improve mood, fatigue and cognition; improve gastrointestinal disorders	decreased weight; device related infections; device dislocations; device issues; polyneuropathy

Although side effects will remit after drug withdrawal, antipsychotics in PD patients should be used cautiously [39]. Nonbenzodiazepine hypnotics like eszopiclone are widely-used sleeping pills in insomnia. They have lower risks to suppress breathing and do not need too much specialized monitoring [43, 40]. 3-5mg melatonin and 2mg melatonin sustained release can also significantly improve the subjective quality of sleep, although objective sleep quality is not improved in polysomnography [44]. Agomelatine is an effective melatonergic antidepressant that has dual treatments for both sleep disorders and depression. It may have considerable therapeutic potential in PD patients for sleep problems and mood disorders that often occur at the same time [45]. Zonisamide has been used as a safe and effective add-on treatment when general PD therapy is not satisficatory to control motor/non-motor symptoms of PD. Its mechanism is related to inhibition of monoamine oxidase-B, modulation of the levodopa-dopamine metabolism and DA receptor expression [46]. Studies have also shown zonisamide can improve PD motor symptoms, sleep disturbances, impulse control disorders (ICD), depression, and cognitive impairment, making it a suitable choice for complex conditions of the elderly [46, 47].

2.2. Restless Legs Syndrome (RLS)

RLS is described as an uncontrollable urge to move the legs in rest or inactivity, usually accompanied by unpleasant sensations and can be partially or totally relieved by movements [56]. The prevalence of RLS in general population is 4-10%, but the chance in PD patients (untreated and treated) is about two to three times more than that [57] .The prevalence of RLS in PD increases with the course of PD and the duration of PD drug treatment [58]. Although RLS has a high prevalence in PD, it is often overlooked. Some studies found that up to 40% of PD patients experience similar leg restless, but only 15% of them meet the diagnosis criteria of RLS [59] And the real prevalence rate may be much higher than expected because PD and RLS share the same effective treatment with dopaminergic drugs, which may cover up RLS symptoms [60]. Compared to those without RLS, PD patients with RLS have significantly greater anxiety severity, depression severity and pain severity, which are associated with severe disability [61].

The pathologic mechanisms of RLS are not fully understood. DA dysfunction, iron deficiency, and genetic defects seem to play important roles in RLS pathology [62,63] but there are still questions about the pathology of RLS in PD. Specifically, no difference was seen in iron metabolism in PD patients with and without RLS, and dopaminergic neurons outside the blood-brain-barrier seemed to play an important role in RLS pathophysiology in PD patients, indicating idiopathic RLS and RLS in PD might have different pathogenesis [56, 64, 65] What's more, functional imaging study showed diminished regional homogeneity and functional connectivity within the precentral and postcentral gyri in PD patients with RLS, which implies that the functional abnormalities in sensorimotor network may disrupt the lateral pain pathway and contribute to RLS pathophysiology in PD [66]. RLS can also be a side effect of certain drugs like some antidepressants and neuroleptics [67]. Female, cognitive dysfunction and worse QOL are also reported to be associated with RLS in PD [60, 68-70].

Levodopa and DA agonists are reported to alleviate RLS in PD [56] (Table **2**). Levodopa is the gold standard for PD treatment and is well tolerated for most PD patients. But it still has a risk of RLS symptom aggravation due to the augmentation syndrome, or RLS symptoms might rebound in the morning because of its short half-life [71]. Thus, the lowest-effective dose of levodopa using intermittently is

Table 2. Pharmacological treatments of RLS in PD patients.

	Recommended Dose	Benefits	Side Effects
Levodopa	200-300mg [80]	improve nighttime RLS symptoms; improve overnight motor and non-motor symptoms; reduce pain	aggravate RLS; symptoms rebound in the morning; dyskinesia
Dopaminergic agonists			
Pramipexole	0.375- 4.5 mg [74]	improve nighttime RLS symptoms; improve overnight motor and non-motor symptoms; reduce pain	visual hallucinations; daytime somnolence; sudden sleep attack; fatigue; nausea; ICD; orthostatic hypotension; edema
Ropinirole	0.25-4.0mg [81]	improve nighttime RLS symptoms; improve overnight motor and non-motor symptoms	aggravate RLS; dyskinesia; headache; dizziness; daytime somnolence; nausea; leg edema
Rotigotine	2-16mg [82]	improve nighttime RLS symptoms; improve overnight and early morning motor performance; reduce nocturia	local site reactions; dyskinesias; headache; dizziness; daytime somnolence; fatigue; nausea
$\alpha 2\delta$ ligands			
Gabapentin	800 mg (100 mg for patients >65 years initial daily dose) (200 mg for patients with uraemia) [56, 83]	improve nighttime RLS symptoms; reduce pain	dizziness; daytime somnolence; peripheral edema
Pregabalin	150-450 mg (50 mg for patients >65 years initial daily dose) [56, 83]	improve nighttime RLS symptoms ; improve subjective nighttime sleep; reduce pain	dizziness; daytime somnolence; headache; fatigue
Gabapentin enacarbil	600-1200 mg (300 mg for patients >65 years initial daily dose) [56, 83]	improve nighttime RLS symptoms; reduce pain	daytime somnolence; headache; fatigue
Others			
Apomorphine	18- 48 mg [84]	improve nighttime RLS symptoms; reduce pain and spasm	rebound morning stiffness; subcutaneous nodules

recommended [62]. DA agonists are able to provide continuous effective doses in blood and are widely used in the treatment of RLS [72]. They should be administered 2 to 3 hours before bedtime to relieve RLS in PD [73] but DA agonists also have many side effects. For example, high doses of dopaminergic agonists can result in visual hallucinations that are dose-related [74]. Pramipexole has a higher risk of ICD compared to other DA agonists due to its affinity for the D3 receptor [74]. In PD patients with older ages, cognitive dysfunction and ICD, some studies suggest that DA agonists should be avoided and only levodopa is recommended; while other recent studies published found DA agonists such as Rotigotine are safe in these patients, and they can bring greater motor and non-motor benefits at the same time [72, 75].

$\alpha 2\delta$ ligands like gabapentin, gabapentin enacarbil, and pregabalin are also demonstrated to be more or equivalently effective than DA agonists in idiopathic RLS. $\alpha 2\delta$ ligands can cause depression and weight gain, thus DA agonists are usually considered as the initial treatment for RLS [76]. While $\alpha 2\delta$ ligands do not have dopaminergic problems like augmentation, ICD, severe daytime somnolence, and hallucinations, and are more suitable for moderate to severe RLS patients [56], evidence also shows that, for severe RLS cases which $\alpha 2\delta$ ligands do not work, DA agonists are still effective [76] but studies about the efficacy of $\alpha 2\delta$ ligands on PD patients with RLS are still limited. Considering their quite common side effects, $\alpha 2\delta$ ligands should be used with caution in PD patients. Apomorphine is also effective for PD patients with RLS in some studies. It can relieve pain and spasm overnight and is good for improving the microstructure of sleepbut it should only be regarded as a supplementary treatment when other treatments are ineffective in advanced PD [56]. Cabergoline 2-3 mg/d has a good evidence on improving nighttime RLS symptoms, but considering its severe side effects such as cardiopulmonary fibrosis, it is not currently used in clinic [72]. Iron therapy lacks enough evidence in treating RLS in PD, and might even cause opposite effect since the pathology PD seems to associate with oxidative damage caused by iron accumulation in the SN [77]. Opioids have been shown to be effective for refractory idiopathic RLS, but there is no research exploring their effects on PD patients with RLS. There are also reports about some other drugs treating RLS in PD, such as istradefylline, safinamide, and levodopa-carbidopa intestinal gel [56, 78, 79]. but the sample sizes of related studies are too small to provide reliable conclusions.

2.3. REM Sleep Behavior Disorders (RBD)

RBD is a precursor of α-synucleinopathy in many neurodegenerative diseases [85]. It is characterized by muscle atonia loss during REM sleep and can cause dream enactment behaviors [86]. RBD is usually suspected through patient's self-report or spouse interview, and definitive diagnosis of RBD is made by polysomnography. Only 1% of adults had RBD, but this number for PD patients ranged from 30.0 to 62.5% [2]. RBD can appear before or after the development of motor symptoms of PD [87]. Prospective clinical studies have suggested that PD patients with RBD were disabled earlier than those without RBD. RBD can be regarded as a sign of motor function deterioration and poor prognosis [88-90]. Compared to those without RBD, PD patients with RBD are generally prone to experiencing more severe and complicated motor and non-motor symptoms [91]. Specifically, PD patients with RBD are more susceptible to more severe motor symptoms, more severe autonomic dysfunction, ICD, and require higher doses of levodopa therapy [19, 92]. They are also at a higher risk of non-motor symptoms, including constipation, hallucination, depression, and cognitive impairment [93-97]. All of these factors make RBD patients have a relatively lower QOL, and emphasize the importance of controlling RBD in PD patients [98].

RBD might result from dysfunction of the brainstem nucleus and brainstem locomotor centers [32]. A neuromelanin-sensitive MRI study demonstrated decreased signal intensity within the locus coeruleus/subcoerulus, which may involve in maintaining REM muscle atonia, and a corresponding increase in muscle tone during sleep in those individuals with RBD [99]. Numerous studies have uncovered that PD and RBD share common pathogenesis, such as chronic neural tissue damage and aberrant expressions of microRNAs [100, 101]. Molecular imaging also shows that PD with RBD have lower striatal DA transporter activity within the caudate and putamen comparing to PD without RBD, which might imply DA system is also involved in symptomatic progress of RBD in PD [102]. These findings may explain why the prevalence of RBD in PD patients is so high. In addition, PD patients with co-existent RBD are characterized by older ages, male, younger ages of PD onset, akinetic/rigid phenotype, falls, higher disease severity, longer disease duration, greater motor fluctuations, and higher levodopa dose [21,103]. Meta-analysis also strongly suggests a relationship between RBD and cognitive impairment, making it a sign of worsening condition in PD patients [104].

Clonazepam, a long-acting sedating benzodiazepine, is the first-line treatment options for RBD [105] (Table **3**). The specific mechanism of clonazepam is not clear yet, and the evidence of its effectiveness for RBD is based on numerous observational studies [86]. Although there is no enough evidence on reduction of objective or subjective RBD severity, clonazepam can significantly reduce phasic electromyography (EMG) activity on polysomnography [106]. Clonazepam mono-therapy was proved ineffective in the patients, a combination of clonazepam with one or multiple other pharmacological agents, such as melatonin, carbamazepine and pramipexole was reported beneficial [105].

There are not too many studies focusing on treatment effects of melatonin on RBD. Some studies showed 3-12 mg/d melatonin could reduce RBD-related injuries with few side effects, although numbers of RBD events were not reduced [86]. Reports say the pathway that melatonin improves RBD is related to several aspects, such as reducing tonic EMG activity during REM sleep, inhibiting gamma-aminobutyric acid, stabilizing the circadian rhythm, increasing striatal L-dopa bioavailability and modulating skeletal muscles [107]. It is suggested that melatonin can be used as a safe add-on treatment option for PD patients with RBD, especially in the elderly. Prolonged-release melatonin 4 mg/d showed not much effect in reducing RBD in PD, but whether other doses are also ineffective is still unclear [108]. Ramelteon is a melatonin receptor agonist, which has a beneficial effect

Table 3. Pharmacological treatments of RBD in PD patients.

-	Recommended Dose	Benefits	Side Effects
Sedating benzodiazepine			
Clonazepam	0.5-2 mg [105]	reduce RBD events; improve subjective nighttime sleep; reduce phasic EMG activity	worsen OSA; morning sedation; falls; confusion; daytime somnolence
Melatonin and Melatonin agonist			
Melatonin	3-12 mg [86]	reduce RBD-related injuries; improve subjective nighttime sleep	mild headaches; daytime somnolence; fatigue
Ramelteon	8 mg [107]	reduce RBD events; improve subjective nighttime sleep; improve PD motor symptom	daytime somnolence; nausea; lightheadedness; delirium; worsen constipation
Dopaminergic agonists			
Rotigotine	2-16 mg [116]	reduce RBD events; improve PD motor and non-motor symptom; reduce pain	local site reactions; dyskinesias; headache; dizziness; daytime somnolence; fatigue; nausea
Others			
Rivastigmine (patch)	4.6 mg [112]	reduce RBD events; improve subjective nighttime sleep	minor peripheral cholinergic action
Memantine	20 mg [113]	reduce RBD events; improve cognitive function	bradycardia; nausea

on idiopathic and secondary RBD. One study showed ramelteon could not only improve nighttime sleep but also scores of UPDRS-III, which aroused much interest in its mechanism of improving motor symptoms in PD patients [107].

Rotigotine is the only dopaminergic agonist that showed RBD symptom improvement currently in PD patients. Its mechanism is still unclear, but seems to be related to improvement in nocturnal motor symptoms [109]. Pramipexole is reported to affect REM sleep by increasing REM sleep latency and decreasing total REM sleep time [74]. In idiopathic RBD patients, pramipexole markedly reduced the frequency and severity of RBD symptoms and maintained efficacy for up to 25 months [110] but in PD patients with RBD, pramipexol showed lack of effects [111].

Cholinesterase inhibitor rivastigmine was used as an alternative treatment in only one study when melatonin and clonazepam were refractory in PD patients with RBD [112]. Rivastigmine showed beneficial effect in reducing RBD events and improving subjective nighttime sleep, suggesting it might be useful in controlling RBD resistant to traditional treatments. But the sample size of related experiments was too small to draw definite conclusions. Memantine can reduce the frequency of dream enactment and decrease total REM sleep time, which is suggested to be suitable to PD patients with dementia and RBD at the same time [113]. Other drugs like sodium oxybate and zopiclone are also effective in RBD treatment, but their efficacy has not been proven in PD [114].

Antipsychotic drugs like clozapine and quetiapine are also proved to be effective for idiopathic RBD patients and psychotic symptoms in PD patients [85]. But there are no related reliable reports about their effects on RBD in PD. Some drugs should be avoided or reduced because they may aggravate or worsen RBD, such as selective serotonin-reuptake inhibitors (SSRI), benzodiazepines, tricyclic antidepressants, barbiturates and monoamine oxidase inhibitors [115].

2.4. Excessive Daytime Sleepiness (EDS)

EDS is defined as an inability to maintain wakefulness and alertness during the major waking episodes of the day, which results in uncontrolled sleep or sudden sleep attacks [117]. Approximately one-third of PD patients had EDS [118]. EDS, especially the sudden sleep attacks, posed a great risk on PD patients' daily lives when driving cars or operating machines, which limited their activities to a very small life circle and significantly increased disease burden [85]. Some studies believe that EDS is a potential risk factor leading to the deterioration of PD [87] Dhawan *et al*. found EDS was much worse in drug-naive PD patients compared to healthy controls, and became even worse in advanced PD [119]. Although it is often considered to be a complication caused by sleep disturbance at night, some studies suggested that improvement of nocturnal sleep did not modify the daytime sleepiness in PD patients, which pointed out that diurnal sleepiness occurs independently of nocturnal sleep disturbances in PD patients [120].

Pathology of EDS seems to be related to neurodegeneration and extra-nigral pathologic changes [57, 121]. It is also regarded as a marker of widespread neurodegeneration in some studies [57]. Functional imaging studies found PD patients with EDS displayed a trend of increased network connectivity of the posterior default mode network, which was also related to mind-wandering [122]. Many studies have demonstrated that EDS is associated with older age, male, advanced motor impairment, hallucinations, depression, anx-

Table 4. Pharmacological treatments of EDS in PD patients.

	Recommended Dose	Benefits	Side Effects
Melatonin	3-5mg [44, 53]	reduce EDS; improve subjective sleep quality	daytime somnolence ; mild headaches; fatigue
Dopaminergic agonists			
Ropinirole immediate-release	4-30 [127]	reduce EDS; improved subjective quality of sleep	hallucination; dyskinesia; dizziness; daytime somnolence; orthostatic hypotension; leg edema; nausea
Ropinirole prolonged-release	4-30 [127]	reduce EDS; improved subjective quality of sleep	hallucination; dyskinesia; dizziness; daytime somnolence; orthostatic hypotension; leg edema; nausea
Others			
Modafinil	100–200mg [135]	reduce EDS; reduce sudden sleep attack	headache; nausea; dry mouth; anorexia; elevate blood pressure and heart rate
Sodium oxybate	3-9 g [131, 136]	reduce EDS; reduce sudden sleep attack; improve subjective and objective of nighttime sleep; reduce fatigue	suppress breathing; induce OSA; induce insomnia; aggravate EDS; rebound morning tremor; dizziness; nocturia; nausea; reduced alertness
Methylphenidate	10-80mg [132]	reduce EDS; improving PD motor symptoms	insomnia; psychosis; headache; reduced appetite; nausea
Istradefylline	20–40mg [133]	reduce EDS	dizziness; nausea; constipation

iety and longer disease duration in PD patients [32, 123]. In particular, PD patients with cognitive impairment are more likely to develop EDS, and EDS is also a strong predictor of cognitive dysfunction in PD patients [124]. Antiparkinsonian drugs, especially dopaminergic agonists, are believed to increase the risk of EDS in a dose-dependent fashion [118, 125] and a higher levodopa equivalent dose is also associated with a higher incidence of EDS [126]. In addition, EDS is prone to happening at the beginning of new dopaminergic medications, and some patients can be tolerated after several days or weeks, while others cannot.

Melatonin and ropinirole both show effectiveness in reducing EDS in PD patients, which seems to be related to improving nighttime sleep quality [53, 127] (Table **4**) but whether they are still effective in PD patients who only have EDS and sleep well at night is still unclear. Modafinil is a widely used wake-promoting agent that can treat daytime somnolence and sudden sleep attack [128]. It can reduce EDS and sudden sleep attack, although objective measures of sleepiness do not alter [129]. It is well tolerated and has a low prevalence of side effects [130] but in older PD patients with severe cardiovascular diseases, use of modafinil should be cautious because it can elevate blood pressure and heart rate. Sodium oxybate can improve EDS and disturb nighttime sleep at the same time. It can significantly enhance subjective and objective sleep quality [131]. Although Sodium oxybate is well tolerated in most people, its negative effect on breathing at night restricts its usage in PD patients. Methylphenidate can also dramatically reduce EDS in PD patients, as well as improve motor and gait symptoms [132]. PD patients should start using methylphenidate 2 weeks after discontinuation of monoamine oxidase inhibitors [125]. Although efficacy of methylphenidate on EDS is better in PD patients, more RCT studies are wanted. Istradefylline, a selective adenosine A2A receptor antagonist, has been reported to improve EDS in PD patients [133]. It can enhance alertness and increase waking hours. Studies showed it had no negative impact on sleep, which made it a good drug [133]. Caffeine is very common in daily refreshing drinks and believed to be useful on daytime sleepiness. But studies have found no significant benefits on EDS in PD patients [134]. There are also some drugs like Atomoxetine that can reduce EDS in PD patients, but we still lack reliable data for that.

2.5. Sleep Disordered Breathing (SDB)

15 to 76% PD patients can suffer from SDB [32]. It is usually divided into obstructive and restrictive pulmonary dysfunction, which includes obstructive sleep apnea (OSA), upper airway obstruction, central sleep apnea, *et al.* [137]. SDB in PD can also be divided into central, obstructive and mixed, but in most studies, it is not clearly classified [138]. Among various kinds of SDB, OSA is the most common type of breath problem in sleep. OSA is characterized by recurrent partial or complete obstruction of the upper airways during sleep, and it can occur in about 40-60% of PD patients [139]. Clinically, OSA can result in cardiac arrhythmias, nighttime confusion, EDS, refractory hypertension, memory problems and nocturia [137]. While there are also some studies that show PD patients with OSA are less likely to have EDS than non-PD patients with OSA [32]. Timely diagnosing SDB in PD patients and giving proper intervention is of vital importance. Presence of SDB in PD patients can lead to abnormal hypercapnia, resulting in daytime somnolence, fatigue, and cognitive impairment, as well as various cardiovascular, psychiatric and neurologic consequences [57].

The etiology of sleep apnea in PD patients was similar to that of the general population [32]. It has been proposed that pulmonary dysfunction, rigidity of muscles of the chest wall, and changes in posture/kyphoscoliosis may be potential risks for SDB in PD patients [32]. Neurodegeneration was also

proposed as a cause of SDB in PD, but studies showed no correlation between SDB and caudal brainstem serotonergic innervation or striatal dopaminergic innervation [140]. There is also an association between SDB and other types of sleep disorders. For example, OSA can aggravate excessive daytime somnolence in PD patients [141]. In some studies, SDB increases the frequency and severity of RBD events and RBD may render PD patients prone to SDB, although RBD influences sleep-related breathing parameters modestly [142, 143] but in other studies, PD patients with RBD seem to experience lower rate of OSA, which is possibly due to a protective effect of enhanced muscle tone during REM sleep [140].

As for OSA, a meta-analysis has found OSA is associated with increased severity of PD-associated cognitive dysfunction and motor symptoms and may accelerate the neurodegenerative process of PD [139]. High prevalence of OSA in PD patients is also related to many risk factors, such as reduced airway patency regulation, laryngopharyngeal motor dysfunction, autonomic dysfunction, and alterations in motor coordination regulation [144, 145]. Studies have found severe OSA is associated with an obvious reduction in the number of position changes and an increased supine sleep position while sleeping [146]. While in some studies, OSA is related to both the central dysfunction of the brainstem respiratory centers and a peripheral airways involvement [140]. Higher body mass index (BMI) is one of the most important risk factors for OSA in general population. But in PD patients, OSA seems unrelated to the level of BMI and is generally less severe than that of the general population [140]. This may suggest that alteration of the laryngopharyngeal motor control is a distinct mechanism contributing to OSA in PD.

Treatment for SDB in PD was the same as that for the general population. Gold standard treatment of OSA is the continuous positive airway pressure (CPAP) [140]. Long-term use of CPAP can significantly improve subjective and objective sleep quality, as well as daytime sleepiness [147]. Currently, there are very few articles about the effects of pharmacological treatments on SDB, and none of them has shown clear improvement. For example, DA agonists showed an ambiguous impact on SDB [148]. On one hand, DA agonists can reduce SDB severity during REM sleep because of loss of normal muscle atonia; but on the other hand, they seem to enhance the risk of central SDB. Levodopa can improve diaphragm function during acute respiratory failure in patients with COPD, but itself also has a risk of inducing diaphragmatic dyskinesias which may present as marked dyspnoea [138,149]. DBS also does not show significantly impair respiratory drive, but new targets such as the PPN may modify central ventilation control, as PPN directly changes sympathetic activity [150]. Other treatment options include positional therapy to promote sleep in a non-supine position, custom-made mandibular advancement devices, optimization of nasal breathing, *etc.* [140].

3. NON-PHARMACOLOGICAL TREATMENTS

3.1. Sleep Hygiene Education

Sleep hygiene education is the first step to manage sleep disorders in PD patients. Its purpose is to help patients establish healthy sleep habits to improve sleep quality. Many PD patients do not have proper sleep hygiene habits. Some may self-medicate with alcohol to induce sleep, and some go to bed too early and watch TV or play with their phone in bed, which will surely affect the establishment of normal sleep. Exposure to caffeine, alcohol, tea or nicotine less than 4 h before going to bed will also result in poor sleep quality [5]. To improve the sleep-wake cycle and consolidate the effect of pharmacological treatments, it is necessary to maintain regular sleep patterns, increase daytime outdoor activity, limit daytime napping, and avoid prolonged bed rest during non-sleeping hours.

3.2. Exercise

Regular exercise is recommended in PD patients. A meta-analysis including a total of 690 PD patients found exercise had a significant positive effect on subjective sleep quality [151]. Types of exercise should be suitable to patients' disease severity, economic status, personal acceptance and convenience. Generally speaking, exercise can be divided into rehabilitation training under the guidance of doctors or professionals, and general mass sports. Rehabilitation training is more targeted and safer. It can simultaneously implement rehabilitation treatment for sleep disorders, motor and non-motor functions. For example, progressive resistance training can improve insomnia and muscle strength in moderate PD at the same time [152]. There is also a report about benefits of multidisciplinary intensive rehabilitation treatment (MIRT) on sleep disorders in PD, which included a wide range of exercises such as aerobic exercises, relaxation techniques, stretching, stabilometric platform exercises focusing on balance and gait, occupational therapy, speech therapy, hydrotherapy, and robotic-assisted walking training [153]. PD who underwent MIRT showed significant improvement in overall sleep quality comparing to those kept on pharmacologic therapy only without rehabilitation. Slow, smooth movements like Baduanjin Qigong and Tai Chi have proved to improve gait performance and functional mobility in elderly PD patients [154,155]. They can be practiced at home, ensuring the continuity and convenience of treatment. However, research on exercise to improve sleep disorders in PD patients is still very limited, and the exercise modality, frequency, duration, and intensity needed for optimization of sleep is not known [156].

3.3. Deep Brain Stimulation

Numerous pieces of evidence have shown deep brain stimulation (DBS) can improve sleep quality in PD patients[57]. DBS improves sleep-wake disturbances, partly by its direct circuit-mediated effect and partly by an indirect effect such as the resolution of nocturnal motor complications and a reduction of dopaminergic medication [157]. The most commonly used DBS surgeries are bilateral subthalamic nucleus (STN) DBS and pallidal (GPi) DBS. Studies show bilateral STN-DBS surgery can improve RLS symptoms and QOL in PD patients, and these kinds of changes are independent of depression and dopaminergic medication [158, 159]. Although STN-DBS significantly improved subjective sleep parameters in over-1-year follow-up, it could not improve objective sleep parameters like sleep efficiency or sleep architecture [160]. When comparing non-motor effects

of STN-DBS and GPi-DBS, both of them can improve sleep quality, fatigue, mood, and cognition, but only STN-DBS can reduce pain and improve memory and only GPi-DBS are good for cardiovascular and sexual function domains [161] but DBS surgery can also induce unexpected sleep disorders. For example, some studies found that although bilateral STN-DBS could improve the subjective sleep quality, and EDS might be induced or worsen [162]. Studies also reported an increase of complex behavior during REM and changes in REM sleep duration after STN-DBS or GPi-DBS surgery, which can eventually evolve into RBD events [163].

Some studies also recommend DBS of the PPN as a potential surgery to improve sleep disorders in PD patients [164]. Although PPN-DBS is primarily used to improve gait freezing and postural instability in PD and primary progressive freezing of gait (PPFG), it also shows a modulation effect on some non-motor functions, including REM sleep, mood, attention, arousal, sleep-wake cycle and cognition [164-167]. Recent studies have demonstrated PPN is involved in sleep–wake state-dependent central breathing regulation through cholinergic projections to the retrotrapezoid nucleus, which indicates PPN as a potential target for improving SDB in PD patients [168,169]. However, there are also some studies that suggest PPN-DBS may contribute to REM sleep atonia and aggravate RBD in PD patients [165]. In view of the fact that there are too few studies on PPN-DBS to improve sleep disorders in PD, the relevant conclusions need further research.

3.4. Cognitive Behavior Therapy

Cognitive behavior therapy (CBT) is also a good choice for treating sleep disorders in PD. It usually refers to short talking therapy (6 to 12 weeks) helping patients to discover their own problems and establish adaptive behaviors through face-to-face or online [170]. CBT usually includes a combination of sleep hygiene education, stimulus control, relaxation training, and sleep restriction [171]. It commonly performs in a group setting and requires patients to give annual feedbacks [172].

Timed light therapy and bright light therapy are the most commonly-used CBT in the clinic. They are effective in restoring the sleep-wake cycles by exposing to lights regularly as well as increasing melatonin secretion through a rebound effect [173,174]. Studies have found that CBT is useful in alleviating insomnia, EDS, RBD in PD patients, and it is well tolerated and well received by patients [175]. After several rounds of CBT treatment, although objective sleep measured by actigraph did not improve, most patients still reported an improvement of subjective sleep quality [176]. Side effects are often rare and mostly controllable. For example, falling asleep during light therapy should be avoided because it may burn patient's face [51]. CBT is a safe and efficacious treatment, but current studies all show a high drop-out rate. Strategies to increase convenience and enhance treatment effect in PD patients are expected.

3.5 Complementary Therapies

In addition to the afore-mentioned treatment methods, some non-pharmacological treatments have also shown certain therapeutic effects in clinical observations. For instance, massaging the leg and the application of a heat pack received good results in relieving RLS, but the effective time did not seem to be as long as expected [177]. For those with RBD, protective strategies like placing mattresses on the floor or securing windows should be considered because they can help to improve bedroom safety and avoid injuries to both patients and their partners [85, 177]. Psychoeducation, tactile touch and theatre training also showed benefits to sleep quality improvement in PD patients, but relevant researches still lacked strong credibility evidence[178-181].

4. DISCUSSION

Sleep disorders in PD patients sometimes appear alone and sometimes exist in several types at the same time. For example, PD patients with RLS are more likely to develop EDS, while PD dementia patients are more likely to have both EDS and RBD [57]. Different sleep disorders can also affect each other. For example, RBD can reduce the severity of OSA, but they will jointly aggravate the cognitive impairment of PD [182]. In addition to the sleep disorders mentioned above, nocturia and circadian rhythm disorders are also very common clinically, and the treatments basically overlap with the above [123]. What's more, management of comorbid psychiatric symptoms and emotional disorders is also very important to improve sleep quality. Studies have shown that treatment of overnight hallucination, delusion and confusion may consolidate the effectiveness of sleep therapy [183].

When dealing with sleep disorders in PD patients, the following points should be noted:

1. Management of sleep disorders in PD patients should start with sleep hygiene education to help patients establish good sleep habits.
2. Pharmacological treatments of sleep disorders should start with the optimization of antiparkinsonian therapy, especially alternations of dopaminergic agents, to optimize overnight motor and non-motor symptoms.
3. Drugs which can cause or worsen sleep disorders should be withdrawn or replaced.
4. When selecting antidepressants or antipsychotics, those that are effective to both sleep disorders and comorbid emotional disorders or psychiatric symptoms should be chosen.
5. Pharmacological and non-pharmacological treatments can be used alone or at the same time.
6. Treatment convenience and patients' economic condition should be taken into account to have a stable and long-term effect.

Treating sleep disorders in PD patients is a long and iterative process. Supports from family and society are also very important to build up patients' confidence and maintain emotional stability. Improving the sleep problems of PD patients at night can not only improve the QOL of the patients themselves but also reduce the burden on caregivers [184]. Therefore, sleep disorders in PD patients should be identified, diagnosed and intervened as early as possible.

CONCLUSION

Sleep disorders have a high prevalence in PD patients. The most cited sleep disorders in PD included insomnia, RLS, RBD, EDS and SDB, which sometimes appear alone and sometimes exist in several types at the same time. In this review, we discussed some recommended pharmacological and non-pharmacological treatments for sleep disorders in PD. We listed the recommended dosages, benefits and side effect of related drugs, as well as non-pharmacological interventions, including sleep hygiene education, exercise, deep brain stimulation, cognitive behavior therapy and complementary therapies. Management of sleep disorders in PD is a long and iterative process. It is necessary to choose the most suitable treatment with the least side effects in order to have a stable and long-term effect.

LIST OF ABBREVIATIONS

BG	=	Basal ganglia
BMI	=	Body mass index
CBT	=	Cognitive behavior therapy
CPAP	=	Continuous positive airway pressure
DA	=	Dopamine
DBS	=	Deep brain stimulation
EDS	=	Excessive daytime sleepiness
EMG	=	Electromyography
ESS	=	Epworth Sleepiness Scale
GPi	=	Pallidal
ICD	=	Impulse control disorders
LCIG	=	Levodopa-carbidopa intestinal gel
MIRT	=	Multidisciplinary intensive rehabilitation treatment
OSA	=	Obstructive sleep apnea
PD	=	Parkinson's disease
PDSS	=	Parkinson's Disease Sleep Scale
PPFG	=	Primary progressive freezing of gait
PPN	=	Pedunculopontine nucleus
PSQI	=	Pittsburgh Sleep Quality Index
QOL	=	Quality of life
RBD	=	Rapid eye movement sleep behavior disorders
REM	=	Rapid eye movement
RLS	=	Restless legs syndrome
SDB	=	Sleep disordered breathing
SN	=	Substantia nigra
SSS	=	Stanford sleepiness scale
STN	=	Subthalamic nucleus
SWS	=	Slow wave sleep
UPDRS	=	Unified Parkinson's Disease Rating Scale

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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