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Sleep Disorders (S Chokroverty, Section Editor)

Sleep Dysfunction and its Management in Parkinson's Disease

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Opinion statement

Sleep disorders are among the most common non-motor symptoms in Parkinson's Disease (PD). In some cases, symptoms can precede a diagnosis of PD by many years, but otherwise they are commonly encountered during the clinical care of patients. Unfortunately, sleep problems are under-recognized and subsequently inadequately addressed. In our experience, when properly addressed, physicians and patients are quickly aware of the often-debilitating nature of sleep dysfunction. This does not mean that solutions are easily attainable. Sleep in PD is held in a delicate balance, influenced by the disease process, medications, co-morbid symptoms, and a variety of other factors. For this reason, management of sleep in PD often requires an inter-disciplinary approach. Physicians should have an intimate knowledge of the many sleep problems apparent in PD, as well as appreciate the challenge presented by diverse therapeutic options that can both ameliorate and aggravate symptoms.

Introduction

Sleep disorders manifest in diverse presentations, and are often inter-related in complex ways (Fig. 1). For the purposes of this review, we deconstruct sleep symptoms to a core of symptomatic presentations: insomnia, excessive daytime sleepiness (EDS), sleep fragmentation, circadian rhythm

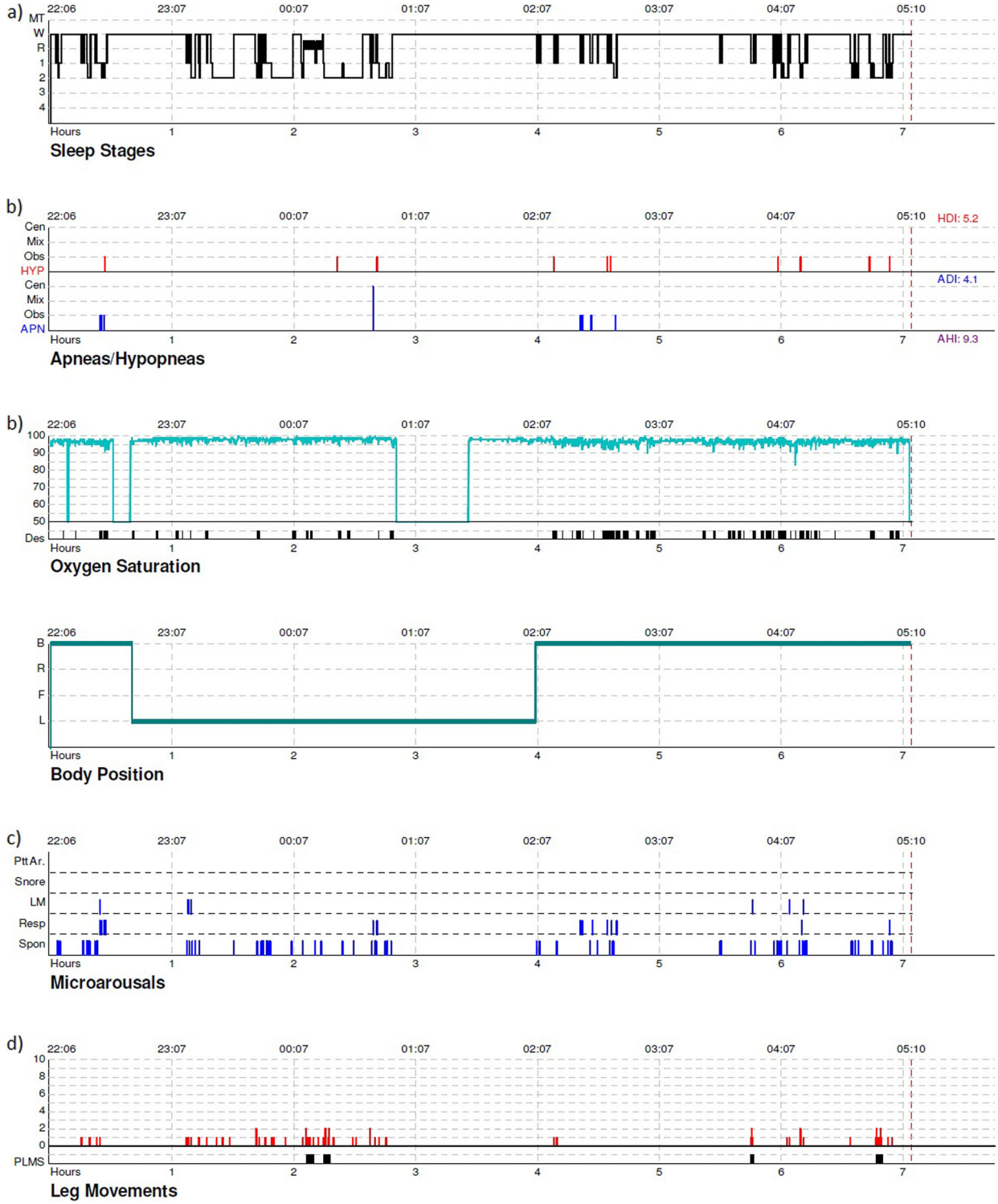

Figure 1. A hypnogram representing multiple comorbid sleep dysfunctions recorded by polysomnography in a PD patient, including (a) marked sleep maintenance insomnia, (b) obstructive sleep apnea with elevated apnea hypopnea index and frequent oxygen desaturations, (c) sleep fragmentation represented by frequent EEG microarousals, and (d) periodic limb movements in sleep.

disorders, restless legs syndrome (RLS) and periodic limb movements in sleep (PLMS), REM behavior disorder (RBD), and obstructive sleep apnea (OSA).

The inability to initiate or maintain sleep is one of the more commonly encountered symptoms in patients. Insomnia is more frequently seen as PD progresses, where increased nocturnal symptoms of rigidity, motor fluctuations, and pain can disrupt sleep [1]. Medications are a common cause for insomnia, where dopaminergic therapy [2], selegiline [3], amantadine [4], and anticholinergic therapy [5] have all been implicated. Of particular importance is the relationship between insomnia and mood disorders such as depression, which have been found to be correlated in the PD population [6•, Class III].

EDS is also frequently encountered in PD, and can be a common side effect of dopaminergic therapy [6•]. Differentiating true daytime sleepiness from feelings of fatigue is important, as it may guide clinical decision making for activities of daily living (ADLs) such as driving [7], and need for further sleep assessments. Screening for EDS with an Epworth sleepiness scale is fast and reliable [8].

Sleep fragmentation may be the most common sleep complaint in PD. In addition to PD symptoms and medication, nocturia is frequently implicated and should always be considered with this presentation [9, Class III]. Hallucinations and altered dream phenomena may also contribute to fragmented sleep [10, Class II]. Of clinical concern, poor sleep efficiency predicts worsening scores of attention and executive function [11•, Class III].

RLS is the most frequent movement disorder in the general population, and has an even higher incidence among PD patients [12, Class III], with an estimated prevalence as high as 12 % [13, Class III], perhaps owing to a suspected common pathophysiology of dopamine and iron dysfunction [14]. The relationship between iron deficiency and RLS is so strong that ferritin levels should be checked in all symptomatic patients, with iron supplementation generally initiated for ferritin levels less than 50. RLS is strongly correlated with PLMS, and together they can contribute to insomnia, sleep fragmentation, and EDS. The four cardinal features of RLS are (1) an urge to move the legs (with or without uncomfortable sensations) that is (2) worse at night, (3) worse at rest, and (4) relieved by movement. Later, a fifth feature is added that specifies that these four cardinal features cannot be solely accounted for as symptoms of other conditions (e.g., RLs mimics) [15]. The worsening of symptoms at night may be a manifestation of a circadian influence. RLS symptoms most commonly involve the lower extremities, but may involve the arms or body, particularly in severe cases.

Disruption to circadian rhythms has been described in PD. Accompanying this is a blunting of the amplitude of melatonin secretion, also correlated to symptoms of excessive daytime sleepiness [16, Class III]. In addition, PD patients treated with dopaminergic medication were found to have a phase-advanced melatonin onset relative to sleep onset, suggesting that dopamine therapy may play a role in circadian disruption [17, Class II]. A phase-advanced circadian rhythm may present as insomnia, particularly as early morning awakenings, or as excessive sleepiness in the early evening. Circadian rhythm dysfunction may also evolve into an irregular sleep–wake cycle, with no clear dominant sleep block and frequent naps throughout the day. As disease progresses, this can be exacerbated by a loss of daytime social cues commonly seen in the elderly and demented [18].

Since first being described in 1986, RBD, characterized by the lack of typical muscle atonia during REM sleep (Fig. 2) and subsequent "acting out" of dreams (please refer to the video associated with this paper), has morphed from a clinical curiosity to a well-defined feature of PD. While being associated with all alpha-synucleinopathy, RBD is well-known to predate frank symptom onset by several years, though it can occur at any time during the course of PD [19]. Polysomnography demonstrating REM sleep without atonia, along with documented abnormal movements or history of injurious behavior, is required for a diagnosis [20].

There is controversy regarding whether PD increases the risk of OSA. While some have suggested an association between the two [21], more recent studies have found no increased risk [22, Class II] and that there is little difference between OSA in PD and in the general population [23••, Class II]. While the possibility of PD increasing the risk for OSA remains unresolved, OSA is a common enough disorder in the typical age of presentation that it should be considered in *any* patient present-

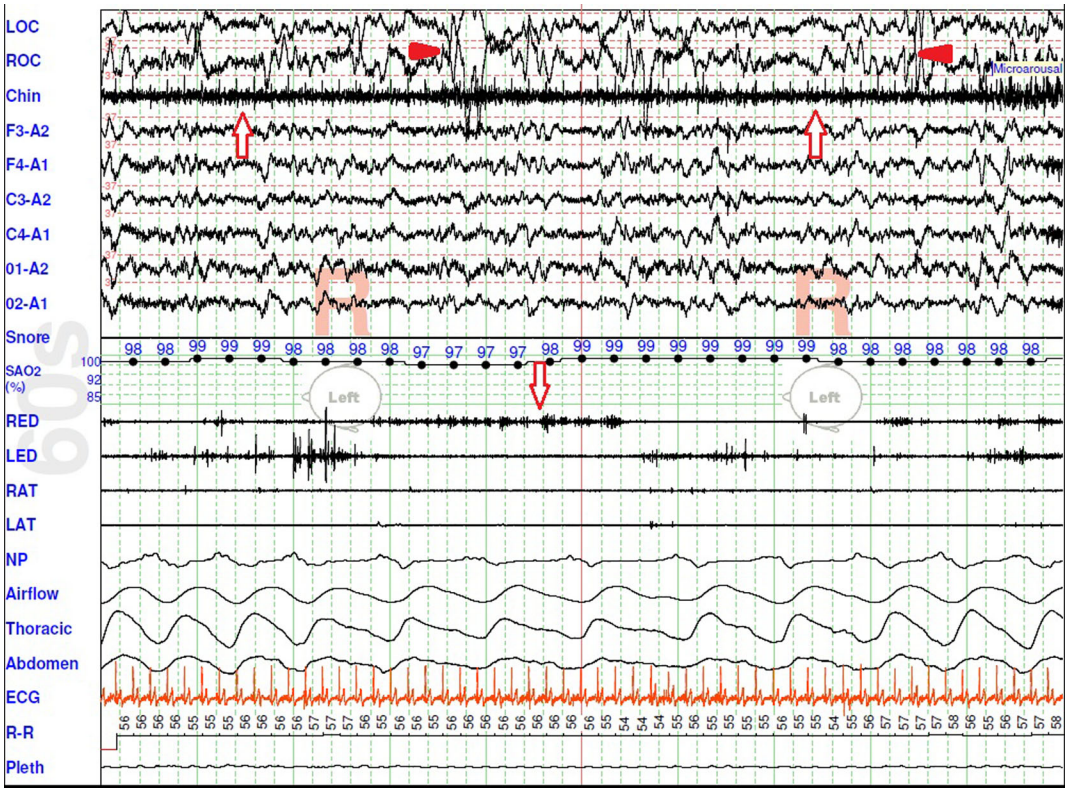

Figure 2. Evidence of REM sleep without atonia on polysomnography, with tonic elevation of tone measured by chin EMG (Chin), and right and left extensor digitorum EMG (RED, LED). Rapid eye movements are evident as sharp vertical deflections in left and right eye channels (LOC, ROC). Note that EMG tone persists (*arrows*) even between these phases of REM activity (*arrow heads*).

ing with sleep fragmentation and daytime sleepiness. Presence of further history and exam findings such as loud snoring, witnessed apneas, elevated BMI, and enlarged neck circumference would further support the need for evaluation by polysomnography.

Treatment

While the goals of treatment—greatest benefit with fewest side effects—are simple, execution can be difficult. Often times, intervention to address one problem can exacerbate another. To address this complex relationship, Table 1 provides an overview of positive and negative effects of each treatment modality. In general, rigorous studies are lacking with respect to sleep disturbances in PD. While not comprehensive, this review aims to address the most common and most well-understood modalities to address the sleep

Table 1. Effects of common therapies on the sleep dysfunction of PD

	Insomnia	EDS	Sleep Fragmentation	RLS/ PLMS	RBD	Circadian Disorder	OSA
Sleep Hygiene	++	+	++	N/A	N/A	N/A	N/A
DBS	+	+/-	+	+	N/A	N/A	N/A
Physical Activity	+	+	+	N/A	N/A	+	N/A
CPAP	N/A	++	++	N/A	N/A	N/A	++
Bright Light Therapy	+	+	+	N/A	N/A	++	N/A
Dopamine	-	-	-	+	+/-	-	N/A
Pramipexole/Ropinirole	+/-	+/-	+	++	+	-	N/A
Rotigotine	+/-	+	+	++	N/A	N/A	N/A
Clonazepam	+	-	+	+	++	N/A	-
Melatonin	++	+	N/A	+	+	+	N/A
Zolpidem/Eszopiclone	++	-	++	-	-	N/A	N/A
Quetiapine	+	+/-	+	N/A	N/A	N/A	N/A
Clozapine	+	+/-	+	N/A	N/A	N/A	N/A
Modafinil	-	++	N/A	N/A	N/A	N/A	N/A
Donepezil	+/-	+/-	-	N/A	+	N/A	N/A
Gabapentin/Pregabalin	++	+/-	++	++	N/A	N/A	N/A

++ FDA approval or significant evidence of efficacy in published literature
+ Evidence of efficacy in published literature
+/- Evidence exists supporting positive and negative effects
- Significant evidence exists supporting adverse relationship
N/A No evidence or unknown treatment effect

symptoms that are pervasive in PD. For simplicity, some similar medications are listed together.

Diet and lifestyle

Sleep hygiene

Though there is limited research in PD patients, addressing basic practices of sleep hygiene is part of the standard management of insomnia, and should be reviewed with any patient with such complaints. Table 2 outlines basic sleep hygiene guidelines.

Behavioral modifications of sleep

Though a full review of behavioral modifications of sleep is beyond the scope of this paper, practices such as stimulus control, sleep restriction, and cognitive behavioral therapy are effective treatments for insomnia. The need for strong patient commitment and frequent follow-up may limit its use in this population.

Table 2. Suggestions for better sleep

- Sleep only as much as you need to feel refreshed the following day
- Get up at the same time each day
- A steady daily amount of exercise can promote sleep, but should not be taken too close to bedtime
- Insulate the bedroom against sounds that may disturb sleep
- Keep room temperature moderate; warm rooms may disturb sleep
- Hunger may disturb sleep; a light snack before bed may help, but avoid greasy or heavy foods
- Avoid excessive liquids in the evening
- Avoid caffeinated beverages, especially in the evening
- Avoid alcohol, especially in the evening
- The use of tobacco disturbs sleep
- Do not take problems to bed
- Use the bedroom only for sleep and sexual activity
- Do not stay in the bed if you feel angry or frustrated, or if you do not feel sleep, as this may worsen sleep

Bed comfort

PD patients may have specific needs beyond those met in standard sleep hygiene review. Use of specialized mattresses, non-restrictive bedding, and bedside commodes or assistive devices may all improve overall sleep quality, and specific needs should be reviewed with the patient and/or caregiver.

Pharmacologic treatment

Levodopa

Levodopa therapy has long been the mainstay of treatment for PD, though its effects on sleep are decidedly more mixed. Polysomnographic studies suggest increasing doses of dopamine prior to bedtime result in worsening sleep efficiency, increasing sleep fragmentation, and decreased REM sleep, along with poorer subjective sleep quality [24]. Not surprisingly then, levodopa use has been strongly correlated to symptoms of excessive daytime sleepiness [25, Class III].

While levodopa was one of the first agents for management of RLS, and has demonstrated effectiveness for up to two years [26], its use may be significantly limited by symptoms of augmentation. Augmentation is characterized by an overall increase in severity of RLS symptoms, with earlier onset of symptoms during the day, faster onset of symptoms when at rest, spreading of symptoms to the upper limbs and trunk, and shorter duration of the treatment effect [27]. Levodopa has also been suggested for treatment of RBD—though this is not endorsed by the American Academy of Sleep Medicine (AASM) (some suggest that levodopa may worsen RBD) [20].

Dopamine agonists

The non-ergot dopamine agonists (DA) ropinirole and pramipexole are both used frequently in the management of PD, both come in standard and sustained-release formulations, and, in standard formulation, both carry FDA approval for RLS and are considered first-line therapy. As with levodopa, there is the concern for excessive daytime sleepiness. Of great clinical concern is the phenomenon of sleep attacks. Characterized by sudden daytime onset of sleep, seemingly without warning or provocation, these episodes can be highly disruptive and potentially dangerous. However, while formal testing of daytime sleepiness symptoms with multiple sleep latency test (MSLT) and maintenance of wakefulness test (MWT) has implicated higher total dopaminergic drug doses [28, Class III, 29, Class IV], they have not correlated to any one specific drug or dosage [30, Class III]. Augmentation is also a concern when treating RLS, though the rates seem to be lower than with levodopa [26]. There is contradictory evidence suggesting that low doses of pramipexole may be effective for RBD [31, Class IV], and that pramipexole has no effect on frequency or severity of PD symptoms [32, Class IV]. The AASM does endorse pramipexole for this use, with caution [20].

Standard dosage Ropinirore and pramipexole doses for RLS are prescribed at low doses for PD, beginning with doses of 0.25–1 mg and 0.125–0.5 mg, respectively. Daytime doses and middle-of-the-night doses may be added, particularly for severe symptoms.

Contraindications: Doses for pramipexole should be adjusted down in patients with renal impairment.

Main drug interactions Additive effects with other dopamine agonists may be seen.

Main side effects In addition to EDS, sleep attacks, and augmentation, DA therapy is known for causing compulsive behaviors, which may manifest in a variety of ways, including gambling, shopping, eating, and sexual behavior. Even at lower RLS doses, incidences of up to 14 % have been suggested [33, Class IV]. All patients initiating therapy should be counseled to monitor for these symptoms. GI side effects are also common.

Special points When increasing DA doses for RLS, one must use caution and consider whether worsening symptoms may be from augmentation owing to DA therapy. In this case, escalating DA doses will lead to increasing symptoms, as well as increasing risk for other adverse effects like EDS. If augmentation is suspected, a medication decrease or switch may be indicated.

Cost/ cost effectiveness Inexpensive

Rotigotine

The rotigotine transdermal patch is a dopamine agonist designed to provide continuous medication across 24 hours, and is approved by the FDA for both PD and RLS. Likely owing to its time-release design, rotigotine has shown particular efficacy for early-morning motor function, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) [34••, Class I], as well as

improvement in daytime fatigue [35]. Rotigotine has shown sustained efficacy for symptoms of RLS for up to five years [36], with a reported rate of augmentation (2.7 %) that is less than levodopa or other dopamine agonists [26].

Standard dosage 1–3 mg patch every 24 hours for RLS, 4–8 mg if for PD

Main drug interactions Additive effects with other dopamine agonists may be seen.

Main side effects Application site reaction is the most common side effect, and can be significant enough to entirely limit use for some patients. Nausea and dizziness are also common, while peripheral edema and falls have been reported. Compulsive behaviors have been reported in up to 7 % of patients [37].

Special points Though risk for augmentation of RLS symptoms is low, it is still present and should always be a consideration.

Cost / cost effectiveness Moderate

Melatonin/Ramelteon

Melatonin, considered a supplement by the FDA and widely available over the counter, and ramelteon, a melatonin receptor agonist available by prescription, may exert several positive benefits on sleep. From here on referred to collectively as melatonin, these medications are beneficial for sleep onset insomnia, due to their hypnotic properties. Melatonin also has efficacy as a chronobiotic, delaying circadian rhythms when given in the early morning, and advancing them when given in the early evening. Lastly, melatonin can be used as primary or adjunctive therapy for the management of RBD [38, 26].

Standard dosage Ramelteon is dosed at 8 mg before bedtime. Melatonin is commonly available from 1–10 mg, though doses exceeding 5 or 6 mg rarely exert greater benefit. When used as a chronobiotic, melatonin doses can be significantly lower (0.5 mg or less) to avoid sedation if given during the daytime.

Main drug interactions Melatonin should not be used with fluvoxamine

Main side effects Headaches, daytime sleepiness, dizziness, and nausea.

Special points Melatonin is commonly found in many over-the-counter (OTC) sleep aides.

Clonazepam

Clonazepam is the treatment of choice for RBD, established enough that textbooks and reviews rarely state more. Recent meta-analysis confirms that it is typically efficacious, often at low doses, and generally well-tolerated [39].

Standard dosage 0.25–0.5 mg starting dose. Can be increased by increments of 0.5 mg to effectiveness.

Contraindications Clonazepam is a CNS depressant, should not be used with alcohol, and can worsen obstructive sleep apnea.

Main drug interactions Should not be used with other drugs that cause CNS depression.

Main side effects Drowsiness, dizziness, impaired coordination, and depression are some of the more common side effects.

Special points Stopping clonazepam, even after long periods of symptoms quiescence, can result in return of RBD behavior. Given its sedating effects, concern

for falls is present and should be considered on a case by case basis. Addiction and withdrawal are infrequent concerns at typical RBD doses, though tapering of medication prior to stopping is advised.

Cost / cost effectiveness Inexpensive

Gabapentin/Pregabalin

The anticonvulsant gabapentin has shown efficacy in treatment of restless legs syndrome. The prodrug gabapentin encarbil, with an extended half-life, is FDA-approved for the treatment of RLS [40]. Pregabalin, which lacks FDA approval, has recently shown to have similar efficacy to dopamine agonists without producing symptoms of augmentation [41••, Class II]. Gabapentin has also been shown to improve sleep efficiency and increase slow-wave sleep [42], indicating it as an effective treatment for insomnia and sleep fragmentation. When taken with these medications' established efficacy for pain, gabapentin and pregabalin have efficacy across multiple sleep complaints common to PD.

Standard dosage Gabapentin can be dosed nightly, starting at 100–300 mg. Titrating doses and daytime doses up to thrice daily can be added for residual symptoms. Timing of pregabalin doses are similar to gabapentin, with doses starting at 50 mg nightly. Gabapentin encarbil is typically dosed at 600 mg nightly.

Contraindications: Medication doses should be adjusted lower in cases of renal impairment.

Main side effects Somnolence, dizziness, headaches, nausea, and irritability may be seen.

Cost / cost effectiveness Inexpensive (gabapentin), moderate to expensive (gabapentin encarbil and lyrica).

Zolpidem/Eszopiclone

The non-benzodiazepine hypnotics potentiate sleep through high affinity for the GABAa receptor. Either alone, or in combination with behavioral therapy, these medications are generally considered safe and effective for treatment of insomnia and nocturnal arousals. However, more recent research has thrown into question their efficacy in the elderly population [43, Class II] as well as their safety, with the FDA recently recommending decreased doses due to concerns over excessive morning sedation [44]. Eszopiclone, with a longer half-life, may be more effective for maintaining sleep through the night, and has been shown to increase sleep time and decrease arousals in PD patients [45, Class IV].

Standard dosage Five or 10 mg for nightly for zolpidem, 2–3 mg for eszopiclone are standard doses, though starting low would be advised in the elderly population.

Contraindications Caution should be used when taken in combination with other sedating medications and alcohol, and in people at risk for falls.

Main side effects Dangerous complex nocturnal behaviors, with an amnestic component, including wandering, driving, and eating, may develop. Overall incidence is estimated at 3 % [46], and the drug should be stopped immediately if these occur. More common side effects include somnolence, headache, dizziness, and nausea.

Cost / cost effectiveness Moderate

Donepezil

The acetylcholinesterase inhibitor donepezil can improve cognition in patients with dementia and PD [47, Class II]. Included in this is improvement in visual and auditory hallucinations that disrupt sleep. Small studies have also suggested the medication, when given in the evening, may improve symptoms of RBD [48, Class IV].

Standard dosage	Donepezil is started at 5 mg and can be increased to 10 mg.
Contraindicationss	Caution should be used for patients with cardiac conduction defects, asthma or COPD, or GI ulcers.
Main drug interactions	Cholinergic agents should be avoided.
Main side effects	May precipitate bradycardia, AV block, syncope, and GI bleeding. Common side effects may include nausea, headache, diarrhea, insomnia, and dizziness.
Special points	Donepezil may promote insomnia and nightmares by increasing REM latency and suppressing REM sleep. Switching to morning dosing may alleviate these problems [49, Class II].

Quetiapine

Nocturnal hallucinations may contribute to insomnia and sleep fragmentation. Quetiapine is an atypical antipsychotic with sedative properties that has been shown to reduce visual hallucinations in PD patients, though it had no effect on sleep times measured by polysomnography [50, Class II]. However, it has shown improvement in subjective symptoms of insomnia and excessive daytime sleepiness [51, Class III].

Standard dosage	Typical doses for sleep range from 25–100 mg at bedtime.
Contraindications	As quetiapine may induce prolonged QT syndrome, patients with this history should avoid usage. The drug may lower seizure threshold.
Main side effects	Common side effects include headache, dizziness, dry mouth, and somnolence. Neutropenia, Stevens Johnson syndrome, neuroleptic malignant syndrome, and tardive dyskinesia have been reported. Atypical antipsychotics carry a black box warning for increased risk of suicidality.
Cost / cost effectiveness	Inexpensive

Clozapine

Like quetiapine, clozapine is an atypical antipsychotic that may be beneficial for visual hallucinations and related sleep disturbances.

Standard dosage	A meta-analysis in PD patients revealed a mean dosage of around 30 mg nightly [52].
Contraindications	Contraindicated in seizure disorders, electrolyte abnormalities, and CNS depression.
Main drug interactions	Fluvoxamine inhibits the metabolism of clozapine, leading to elevated blood levels.
Main side effects	Agranuloctyosis is the major adverse side effect that requires strict monitoring of white blood cell counts. Cardiac toxicity, hypersalivation, seizures, weight gain, and withdrawal are also concerns.

Special points White blood cell count needs to be strictly monitored, first at baseline and then throughout treatment. Due to this, distribution of clozapine is strictly limited in the United States.

Cost / cost effectiveness Cost effectiveness is less than with quetiapine, given the limited distribution of the medication and need for monitoring.

Modafinil

Modafinil is a wake-promoting agent that is FDA-approved for treatment of narcolepsy, shift work disorder, and EDS in the setting of OSA after adequate CPAP titration. Although the mechanism of action is unknown, it is speculated to work at least partially by inhibiting dopamine reuptake [53]. Small trials have shown improved symptoms of fatigue and daytime sleepiness in PD patients [54, Class II; 55, Class III].

Standard dosage 100–400 mg per day, can be divided into twice-daily doses.

Contraindications Modafinil is significantly less likely than stimulants to promote cardiovascular complications such as hypertension and arrhythmias, though it should be used with caution in such cases, as well as patients with left ventricular hypertrophy and mitral valve prolapse.

Main side effects Common side effects include headache, nausea, palpitations, nervousness, dizziness, and insomnia. The severe rash of Stevens Johnson Syndrome has been reported [56].

Cost / cost effectiveness Moderate

Deep brain stimulation

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus (GP) is currently FDA approved for management of advanced PD not otherwise controlled by medication. While DBS is not indicated for treatment of sleep symptoms per se, it may provide some benefit.

Stimulation of the STN has been shown to increase sleep time, stage N3 sleep, and nocturnal arousals, when measured by polysomnography [57, Class III]. Some of these improvements may be directly attributable to improvement in functioning and PD symptoms [58, Class III; 59, Class IV], as well as evidence for improvement in symptoms of RLS [60, Class III]. In addition, improvement in sleep may also be attributable to a decrease in medication usage, and the actual impact of DBS on sleep itself remains unclear.

More recently, targeted stimulation of the pedunculopontine nucleus (PPT) has been considered for severe PD, and has demonstrated improvement in sleep quality and excessive daytime sleepiness [61, Class III].

Exercise

Usage Though exercise is thought to improve sleep quality, studies in PD patients are lacking. One study demonstrated an improvement in sleep disturbances using a multimodal exercise program [62, Class IV]. Though the exact

mechanism is unclear, one can speculate that changes in mood and circadian parameters may be at play.

Special Points In addition to ensuring patient safety, exercise may exert a chronobiotic effect, causing a phase shift in circadian rhythm if performed too early or too late. Any exercise program should be performed at or close to the same time every day.

Other treatments

Continuous positive airway pressure (CPAP)

CPAP use in patients with PD and OSA has been demonstrated to reduce symptoms of daytime sleepiness, as well as decrease nocturnal arousals and increase stage N3 sleep, while decreasing overall apnea hypopnea index (AHI) [63••, Class I

Standard procedure Baseline polysomnography followed by CPAP titration, or single split-night study remain the tests of choice to evaluate OSA in patients with neurodegenerative disease. Class III portable sleep monitoring may be a viable alternative in patients with high pretest probability or those who are unable to tolerate the sleep lab [64].

Special points Close initial follow-up is imperative to establish comfort with CPAP. Patients may require trials with multiple masks, humidity settings, and special features such as pressure ramp and expiratory pressure relief before becoming fully adjusted to the device.

Monitoring CPAP adherence data should be monitored throughout follow-up.

Cost Moderate

Bright light therapy

Timed bright light therapy (BLT) is widely used to address circadian rhythm disorders. Since the primary circadian abnormality of PD appears to be a phase advancement, timing light exposure for the evening is preferred [65, Class IV]. However, morning BLT has been shown to improve symptoms of depression [66, 67].

Standard procedure BLT studied in the literature ranges from 1000–7500 Lux and 30–90 minutes duration. Standard light boxes generally emit up to 10,000 lux and can be used for as little as 30 minutes. Specialized blue wavelength light boxes can be used at similar duration and lower overall Lux output.

Contraindications/Complications BLT is generally safe, but delivery of light out of phase to circadian cycle may compound rather than correct a phase shift. Screening for phase type prior to BLT with a Morningness-Eveningness Questionnaire (MEQ) may be useful.

Special points Effects of BLT are only maintained if therapy is ongoing, with retraction of therapy resulting in resumption of symptoms [65, Class IV].

Cost Inexpensive

Compliance with Ethics Guidelines

Conflict of Interest

Scott J Kutscher and Siavash Farshidpanah declare that they have no conflicts of interest.
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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

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- •• Of major importance

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