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Review article

Sleep disturbance in Parkinson disease

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ABSTRACT

Sleep disturbance is common in patients with Parkinson disease (PD), but it is often undetected due to inadequate history taking and poor self-reporting. Impaired sleep can have a severe impact on health, general well being, and quality of life. Sleep problems in PD have many potential causes, including the direct effect of PD itself, adverse events of anti-Parkinsonian medications, daytime sleep disturbance, age related causes, and other comorbidities. Patients with PD and their sleep partners should be asked about sleep disturbances and other night-time symptoms. Treatment strategies rely on identifying causal factors and need to be tailored to the individual and reviewed regularly.

1. Introduction

This article will review the epidemiology, pathophysiology, and management of sleep disturbance in Parkinson disease (PD). We identified references for this article by searching PubMed database and Google Scholar up to 2011, with Medical Subject Headings (MeSH) terms of "Parkinson disease," "night-time symptoms," "sleep disorders," "elderly," and "dopaminergic therapy." Only English-language literature was included in the search and information was also obtained from international proceedings published in journals specializing in Parkinsonism and related disorders.

In his original monograph, James Parkinson evidently documents sleep-related disturbances associated with PD as: "His attendants observed, that of late the trembling would sometimes begin in his sleep, and increase until it awakened him: when he always was in a state of agitation and alarm".[1] Sleep disturbance in patients with PD may be caused by direct complications of the disease, adverse events from PD medications, age-related alterations in sleep patterns, associated comorbidities, neuropsychiatric complications of PD, or a combination of the above.

In recent times, there has been increased interest in attempting to better qualify and quantify sleep problems in PD. This has led to some understanding and better management of nocturnal symptoms that plague patients with PD. The U.K. National Institute of Clinical Health and Effectiveness (NICE) recognizes the nonmotor symptoms (NMSs) and their management, which encompass sleep-related problems in PD, as an unmet need.[2–4]

Sleep disturbances in PD are often poorly recognized, yet early identification and treatment to maintain or improve quality of sleep can facilitate improvement in motor symptoms,[5–8] improve quality of life (QoL) for caregivers and patients, may delay institutionalization, and may reduce healthcare costs.[4]

Furthermore, poor nocturnal sleep quality can lead to poor daytime functioning and excessive daytime somnolence (EDS), which may, in turn, be associated with increased cardiovascular risk and cognitive impairment.[9,10]

Sleep disturbance is reported by around 25% of spouses of patients with PD.[11] Sleep disturbances in both patients with PD and their sleep partners contribute to caregiver burden and correlate with levels of depression in carers.[12,13]

2. Epidemiology

Estimates of the prevalence of sleep disturbance in PD range from 25%–98%.[5,14] Differences in methodology and selection bias are thought to account for this wide variation. Sleep problems are approximately twice as common in patients with PD (60%–64%) as in age and sex matched controls (33%)[6,7] and are also more prevalent than in those with other chronic conditions.[15,16]

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Sleep disturbance can occur in the early clinical stages of PD and may even predate the onset of PD. There is conflicting evidence as to whether the degree of sleep disorder correlates with Hoehn and Yahr staging of PD.[14,16,17]

The NMSQuest (a validated NMS questionnaire) study reported that sleep problems such as restless legs syndrome (RLS), EDS, and rapid eye movement sleep behavior disorder (REMSBD) are significantly more common in patients with PD compared with controls.[18]

Smith and colleagues[11] reported that 27% of male and 48% female spouses of patients with PD experienced night-time disturbances. The FAQT-study (prospective German cohort study evaluating determinants of quality of life) investigators reported a high prevalence of sleep disturbances in partners of patients with PD associated with[13]:

- Higher Unified Parkinson's Disease Rating Scale (UPDRS) motor scores [odds ratio (OR) 2.8 per 10-point increase, $p = 0.008$]
- Poor sleep in the patient with PD (OR 4.0, $p = 0.008$)
- Male patients (OR 5.0, $p = 0.008$)
- Increasing care-giving frequency (OR 7.4 for daily caregiving frequency, $p = 0.004$)

Neuropsychiatric symptoms such as depression, anxiety, apathy, and cognitive impairment are common in PD and may impair sleep.[19–22] Sleep disorders are also more prevalent in patients with PD who later develop cognitive impairment and may herald more complex subtypes of PD.[23]

In advanced PD, motor symptoms of nocturnal "off" periods, early morning akathisia, dystonia, freezing, and tremor can be very troublesome. Nocturia is reported by up to 62% of patients with PD[18] and has been linked to impaired sleep in up to 70.4% of those with idiopathic PD.[24]

3. Pathophysiology of sleep dysfunction in PD

The pathophysiology of sleep dysfunction in PD is multifactorial, complex, and, as of yet, incompletely understood. Sleep dysfunction, like other nonmotor features of PD, is known to predate the onset of motor dysfunction. REMSBD and depression might precede the expression of motor features by more than a decade.[2,25] This has often led to misdiagnosis, inappropriate referrals, and delayed treatment.[26]

3.1. Lewy body pathology and dopamine dysfunction

The progression of Lewy body pathology in PD closely correlates with the occurrence of NMSs predating the motor dysfunction,[27,28] suggesting that Lewy body deposition and neuronal dysfunction commence in the olfactory bulb and lower medulla. Motor features appear only when the substantia nigra pars compacta is affected by loss of dopaminergic neurons. The axons from the key dopaminergic areas (substantia nigra pars compacta, ventral tegmental area, and the hypothalamus) project extensively to form the four main pathways—the mesocortical, mesolimbic, nigrostriatal, and tuberoinfundibular pathways—that mediate NMS such as sleep, cognition, and pain.[21] ^{11}C-raclopride positron emission tomography (PET) imaging in patients with PD has demonstrated dopamine dysfunction in the hypothalamus.[29]

3.2. Degeneration in raphe nucleus and locus coeruleus

As sleep disturbance may precede motor dysfunction, it is postulated that degeneration occurs in areas such as raphe nucleus (serotonin) and locus coeruleus (noradrenaline) thereby constituting the pre-clinical stages 1 and 2 of Braak's pathological staging of PD.[27] These nuclei play a critical role in the sleep-wake cycle and thalamocortical arousal, and their degeneration leads to disruption of basic sleep architecture [both rapid eye movement (REM) and non–REM], thereby manifesting as insomnia, parasomnias and hallucinations.[30,31]

3.3. Influence of the pedunculopontine and retro-rubral nuclei on REMSBD

The pedunculopontine nucleus and the retro-rubral nucleus have been implicated in the pathogenesis of REMSBD due to their strong influences on REM atonia and phasic generator circuitry.[31]

3.4. Destabilization of the flip-flop-switch regulation of sleep-wake cycle

Saper[32] proposed the flip-flop-switch pattern of regulation of the sleep-wake cycle, describing that the brain could be either "off" (asleep by activating the ventrolateral preoptic area, the sleep promoter) or "on" (in quiet wakefulness with the activation of the tuberomammillary nucleus, the wake-promoting area along with locus coeruleus and the raphe nuclei). The suprachiasmatic nucleus regulates the internal rhythm between the two switches. The hypothalamic peptide that is virtually undetectable in narcolepsy; hypocretin 1 (orexin) is thought to have a complex relationship in the dopaminergic systems within the basal ganglia and may function as an external regulator of the flip-flop switch promoting wakefulness.[31,33] Destabilization of this switch and its regulators occur in PD secondary to dopaminergic dysfunction and neuronal degeneration, resulting in rapid transitions to sleep intruding on wakefulness. The hypothesis of dopaminergic medications reducing levels of hypocretin 1 and producing sleepiness could not be confirmed by cerebrospinal fluid (CSF) analysis in three patients with PD and EDS associated with dopamine agonist (DA) use.[34]

3.5. Age-related changes

In addition to these PD related changes, there are age-related changes in sleep and circadian rhythm. Older people often sleep for shorter periods of time at night and have more daytime naps than their younger counterparts. Sleep architecture also alters with ageing, with reduced Stages 3 and 4 of non–REM sleep. Around 40% of older people experience some form of sleep disturbance and these are more common in those with physical and psychological problems.[35]

4. Causes

The main causes of nocturnal sleep problems and EDS are nocturnal motor symptoms of PD, adverse effects of medications used for PD, NMSs of PD (including neuropsychiatric symptoms, sleep dysfunction, dysautonomia), other comorbidities, concomitant medications, and age-related alterations in sleep patterns (Tables 1 and 2).

4.1. Motor function/treatment related

The longest time patients with PD spend without any pharmacological intervention is at night. This is to avoid the stimulating effect of dopaminergic therapy, which may result in impaired sleep. However, the long period without any drug treatment can result in nocturnal "off" periods, the resultant akinesia leading to difficulty turning in bed, stiffness, early morning dystonia, and tremor. There may also be an increase in NMSs of pain and muscle cramps that

Table 1
Causes of night-time problems in Parkinson disease.

Motor function related	Akinesia (difficulty turning)
	Restless legs syndrome
	Periodic limb movements of sleep
Treatment-related motor function	Nocturnal "off'-period-related tremor
	Dystonia
	Dyskinesia
	"Off"-period-related pain
	Paraesthesia
	Muscle cramps
Neuropsychiatric/ parasomnias	Depression
	Anxiety (generalized, panic attacks, social phobia)
	"Off'-period-related panic attacks
	Apathy
	Cognitive dysfunction
	Vivid dreams
	Altered dream content
	Nightmares
	Night terrors
	Sleep talking
	Nocturnal vocalizations
	Somnambulism
	Hallucinations
Sleep dysfunction	Insomnia (sleep-onset, sleep-maintenance)
	Rapid eye movement sleep behavior disorder
	Non–rapid-eye-movement-related sleep disorders
	Akathisia
Autonomic	"Off"-period-related incontinence of urine
	Nocturia
	Nocturia with secondary postural hypotension
Medications	

Adapted from Chaudhuri KR. Nocturnal symptom complex in PD and its management. *Neurology* 2003;61(**Suppl 3**):S17–S23.

should respond to dopaminergic therapy. Sleep may also be fragmented due to night-time "off" dyskinesias and akathisia (restless legs).

Treating these nocturnal "off" symptoms has to be balanced against the alerting/arousal effects of dopaminergic therapy which might generate insomnia, vivid dreams, and "on" dyskinesias.

4.2. Neuropsychiatric disorders

Depression affects around 40% of patients with PD.[37] The symptom complex of depression in PD may be hard to distinguish from early cognitive impairment[22]; it is linked to dysfunction of dopaminergic, serotoninergic, and norepinephrinergic pathways in the limbic system.[38] Depression is independently associated with sleep disorders (e.g., early morning wakening) and can also exacerbate motor and drug-related symptoms.

Anxiety disorders often coexist with depression and motor fluctuations and are usually the result of neurobiological or neuropeptide abnormalities associated with PD.[20] These may manifest as generalized anxiety states, panic attacks, and social phobia. If related to a dopamine-dependent "wearing off" state, anxiety can respond to treatment of the motor dysfunction with dopaminergic therapy.[39] Some anxiety states are independent of the dopaminergic state these are usually more difficult to treat but may respond to anxiolytics or antidepressants.

Apathy is a specific symptom of PD, occurring with or without depression, for which a dopaminergic basis is possible. The Geriatric Depression Scale can help distinguish true depressive symptoms from those of apathy.[40,41] Apathy is generally associated with EDS.

Cognitive dysfunction is usually a feature of advanced PD, but can occur early as a frontal dysexecutive syndrome, manifesting as impaired adaptive response against competing alternatives.[42] Visuospatial and visuoperceptual deficits have also been noted in patients with PD.[43] Mild cognitive impairment (MCI) has been identified in 72/126 (56%) of patients with early PD.[44] The caudate and corticostriatal pathways are implicated in early cognitive changes.[45] Brain metabolism and dopamine uptake is impaired in cortical targets of striatal dopaminergic targets.[46,47] Sleep disturbances related to cognitive impairment include EDS, nocturnal hallucinations, and altered dream content.

Table 2
Non–Parkinson disease-related causes of night-time problems in the elderly.

Age-related sleep changes	Altered sleep architecture
	Altered circadian rhythm
Medical or health problems	Sleep apnea
	Periodic limb movements of sleep
	Pain (chronic arthritis)
	Heart failure
	Palpitations
	Frequency of micturition
	Gastroesophageal reflux disease
	Constipation
	Allergies
	Mental disorders, e.g. depression, anxiety
	Dementia (increases non–rapid eye movement light sleep and decreases in non–rapid eye movement deep sleep)
Medications	Beta-blockers
	Sleeping medications (e.g. benzodiazepines)
	Sedative antidepressants and antipsychotics
	Theophylline and caffeine
Other factors	Nicotine, alcohol
	Sedentary behavior
	Daytime napping
	Sadness or bereavement/stress

4.3. Sleep dysfunction

Sleep architecture studies in PD reveal reduced total sleep time and sleep efficiency, sleep arousals and fragmentation, while circadian variation of symptoms are also reported enabling classification into the "morning better," "morning worse," and a non-affected group.[36,48]

REMSBD is a parasomnia with a population prevalence of 0.5%.[49,50] REMSBD causes loss of the normal skeletal muscle atonia during REM sleep. This enables patients to enact their dreams, which can be unpleasant or vivid. Spouses and partners report vocalizations (talking, shouting and vocal threats) and abnormal movements (limb jerks, falling out of bed, and violent assaults). This may result in injury to the individual or their sleep partner. REMSBD disturbs the sleep of patient and partner, impacts on QoL for patient and partner, often results in poor quality sleep, so there is EDS, and it can endanger the sleep partner.[51]

The diagnosis can usually be made from the clinical history but may sometimes require polysomnography with video telemetry for confirmation. A total of 11 out of 33 consecutive patients with PD were diagnosed as having REMSBD by a combination of structured clinical interview and polysomnography; clinical interview alone would not have identified half of these patients.[51,52] REMSBD may predate the diagnosis of PD and represent a preclinical stage: 11 of 29 men aged $\geq$ 50 years developed a Parkinsonian disorder 3.7 ± 1.4 (standard deviation) years after the diagnosis of REMSBD and 12.7 ± 7.3 years after the onset of REMSBD.[53] REMSBD seems to be associated with degeneration of lower brainstem nuclei, such as the pedunculopontine nucleus and locus coeruleus which have connections with the dopaminergic ventral tegmental area in the midbrain. These observations are consistent with the Braak hypothesis[27] that the preclinical Stages 1 and 2 of PD start in the olfactory and medullary area of the brainstem and progress rostrally. Individuals with olfactory disturbances and REMSBD have

also been shown to be at increased risk of developing PD.[54] After diagnosis of REMSBD in patients without parkinsonism, Postuma and colleagues reported the estimated 5-year risk of developing PD after being diagnosed with REMSBD is 17.7% and the 10-year risk 40.6%.[55] REMSBD may also be associated with other nonmotor manifestations of PD, e.g., hallucinations, orthostatic hypotension, and dementia.[56]

Insomnia is probably the most common sleep disturbance in patients with PD.[57] It is often multifactorial and may be related to motor, NMSs, depression, anxiety, obstructive sleep apnea, urinary problems, or any combination of these. Sleep-onset insomnia (difficulty in falling asleep) is usually associated with PD itself, but can occasionally be brought on by dopaminergic therapy, e.g., selegiline may delay onset of sleep as a result of its amphetamine metabolites. Amantadine and anticholinergics may produce an alerting effect and selective serotonin reuptake inhibitors (SSRIs) need to be avoided at bedtime given that they may impair sleep onset.[48] Sleep-maintenance insomnia (difficulty in maintaining sleep for periods of time) is usually a result of akinesia and other "off"-state related motor and NMSs, e.g., RLS, periodic limb movements of sleep (PLMS), nocturia, and reversal of sleep patterns.[5,58]

RLS is an urge to move the legs, to relieve unpleasant or uncomfortable sensations brought about by rest, which tends to worsen in the evening.[59] It is associated with insomnia, anxiety, and depression.[60] RLS has a two-fold increase in prevalence in PD compared with the general population (although the diagnostic criteria for RLS have not been validated in PD)[61] and along with PLMS (repetitive, rhythmic jerking movements of the limbs during sleep) is known to cause frequent sleep disruption.[62,63] In advanced PD of the akinetic rigid phenotype, akathisia is common (and symptoms are similar to those of RLS) probably related to changes in the mesocortical dopamine pathways.[64] PD often precedes RLS suggesting RLS may be a secondary phenomenon. RLS may be associated with iron deficiency and in such cases will respond to iron replacement therapy. RLS may also be associated with renal impairment.

EDS describes a tendency to fall asleep in the daytime, which may interfere with social functioning, cognition and contribute to accidents and falls.[65,66] Care must be taken to differentiate EDS from symptoms of chronic fatigue that also occur in PD. EDS can occur in the early stages of PD[67] and may even predate the diagnosis of PD.[68] EDS has a higher prevalence in patients with PD than in controls (affecting approximately 50% of patients with PD), does not appear to be age-related, and is more severe in the later stages of PD.[69,70] Thus, EDS may be related to the underlying neurodegeneration.

The manifestations of EDS are profoundly variable; some feel sleepy and slowly drift off to sleep, while others have rapid-onset sleep without any preceding drowsiness resembling narcolepsy.[31]

There is evidence of a correlation between EDS and the use of dopamine agonists, but not with levodopa.[65,71–73] So-called "sleep attacks" (falling asleep without a prodrome) are rare and may be associated with dopamine agonist usage.

In most instances EDS will be multi-factorial due to a combination of sleep fragmentation, depression, coexistent sleep apnea, and the use of hypnotics, antidepressants, and DAs.

4.4. Nocturia

Nocturia is a common problem in older age. However, symptoms of overactive bladder syndrome are more common in patients with PD than age-matched controls and these symptoms worsen as PD progresses.[18,74,75] Both the presence and severity of urinary symptoms appear to correlate with the extent of dopaminergic neurone depletion.[76]

The high incidence of nocturia in patients with PD is likely due to a combination of reduced bladder capacity, increased urine formation at night, impairment of sleep due to "off" period, urgency, and detrusor overactivity.

4.5. Obstructive sleep apnea

Snoring and obstructive sleep apnea (OSA) are three times more common in patients with PD as controls and may occur in up to 50% of patients with PD.[77] OSA may also occur in conjunction with RLS, PLMS, or REMSBD.[67,69] Patients with PD with OSA typically have a normal body mass index unlike patients without PD but with OSA.[69]

Reduced neural output causes relative weakness of the muscles around the upper airway leading to partial or complete airways collapse. The resultant hypoxia promotes sufficient awakening to stimulate breathing. These microawakenings leave the individual in a state of light sleep, which is nonrestful, so he or she is fatigued and somnolent during the day. His or her sleep partner may be aware of the patient's loud snoring, periods of apnea, and gasping. Correct diagnosis is essential for these patients to have specific and targeted treatment.

OSA can be diagnosed by overnight oxygen saturation monitoring and polysomnography.[78] It can be treated by overnight continuous positive airway pressure (CPAP).

4.6. Other causes

It is all too easy to ascribe every symptom to the PD. A thorough search should also be made for non–PD related causes of nocturnal disturbances in patients with PD, e.g., other medical ailments and adverse events of medications.

5. Assessment of sleep disturbance

Given the varied nocturnal symptoms in patients with PD, the first step toward management is identification of such problems by qualitative and quantitative means. Specific questioning of patient and sleep partner should include:

- Sleep pattern, including insomnia, EDS, and "sleep attacks"
- RLS
- Vivid dreams and hallucinations
- Acting out dreams (REMSBD)
- Nocturnal motor symptoms (including PLMS)
- Nocturia and other urinary symptoms
- Medication (PD and non–PD)
- Comorbidities
- Snoring and apneic attacks

The gold standard for quantification of sleep disorders is polysomnography and sleep latency tests; however, these are costly and often of limited availability.

5.1. Scales and measures

Sleep dysfunction can be assessed (presence and severity) by several scales, of which six are recommended by the Movement Disorder Society (MDS).[79] This is shown in Table 3. These are all screening tools that cannot diagnose specific sleep disturbances in PD but can assess severity and response to treatment.

The Parkinson's Disease Sleep Scale (PDSS) is a 15-question visual analogue scale that can be used at the bedside and is available in five languages (English, German, Italian, Swedish, and Spanish).[80] It has robust test–retest reliability and good

Table 3
Sleep scales in Parkinson disease.

Scale	Number of items to complete	Assessment details
Parkinson's Disease Sleep Scale	15	Nocturnal disturbance and excessive daytime somnolence *Time scale: Over previous weeks*
Pittsburgh Sleep Quality Index	19	Sleep quality *Time scale: Over the previous month*
Scales for Outcomes in Parkinson's Disease Sleep Scale	12	Sleep quality, daytime sleepiness and night-time sleep disturbances *Time scale: Over the previous month*
Epworth Sleepiness Scale	8	Daytime sleepiness presence and severity *Time scale: In recent times*
Inappropriate Sleep Composite Score	6	Risk of sudden onset of sleepiness while driving
Stanford Sleepiness Scale	1	General level of daytime sleepiness *Time scale: At that specific moment in time*

discriminatory powers between patients with PD and healthy individuals.[58] The PDSS has recently been revised and validated (PDSS-2) to include an extended spectrum of nocturnal disturbances, and may better reflect response to treatment.[81] The 12-item Scales for Outcomes in Parkinson's disease-Sleep (SCOPA-SLEEP) scale assesses both night-time and daytime sleep; though validated, it does not address some of the night-time symptoms of PD very well.[82] The Epworth Sleepiness Scale (ESS) is very specific for assessing EDS in eight daily situations but lacks test–retest reliability and cross-cultural differences.[83]

Depression may be assessed by a variety of scales, such as the Geriatric Depression Scale (GDS), Montgomery-Asberg Depression Rating Scale (MADRS), and the Zung self-rating depression scale. Anxiety may be assessed using the State Trait Anxiety Inventory and the Hospital Anxiety and Depression (HAD) scale.

Objective measurements of sleep in PD patients include polysomnography (PSG), multiple sleep latency tests (MSLT) and maintenance of wakefulness test (MWT). PSG includes objective assessment of the entire gamut of standardized measurements of brain activity, respiratory functions, eye movements, and electromyography (EMG) to measure sleep architecture and provide quantitative measurements of sleep disturbance, which are useful for diagnosing sleep apnea, PLMS, and REMSBD. The MSLT and MWT are useful for evaluation of EDS and the ability to remain awake.

5.2. Evaluation of nocturnal sleep disorders

Clues to the presence of nocturnal sleep disturbances may be obtained by interviewing the bed partner. Snoring and respiratory pauses would suggest OSA, whereas kicking during the night would point to PLMS and dream enactment behaviors suggest REMSBD. However, the differentiation of these conditions is not always clear-cut as there is considerable overlap in symptomatology. PSG is essential for diagnosis of PLMS, which is an intermittent, rhythmic movement of the legs mainly occurring in non–REM sleep. Although PSG is the gold standard, thorough interviews of the patient and their sleep partner are invaluable bedside tools.

5.3. Evaluation of EDS

It is generally assumed that EDS worsens nocturnal symptoms and vice versa. However, EDS can occur without significant nocturnal problems.[48] A good pointer for EDS is an elevated ESS score, which predicts the occurrence of sleepiness and dozing while driving.[84] Subjective reports of EDS underestimate those diagnosed by MSLT.[85]

6. Treatment options

The approach to managing sleep disturbances in patients with PD (especially in the older population) requires a holistic view,[74] bearing in mind that some of the symptoms may arise from the interplay of other comorbidities. Well being of the sleep partners or carers is also important in formulating a treatment plan. Ensuring good sleep hygiene is a key element to managing all sleep disturbances (Table 4).[86]

Bed rails and straps can help make turning in bed easier as can silk sheets. Spouses of patients with REMSBD may need to move in to a separate bed or bedroom as may those of patients with severe snoring.

Treatment should be targeted at the causal factors disrupting sleep, whether PD or comorbidity related and may consist of non-pharmacological as well pharmacological strategies (Table 5). However, the patient should be warned that full resolution of symptoms is unlikely and that a strategy to improve one symptom may worsen another.

6.1. Nocturnal sleep disturbances

6.1.1. Sleep fragmentation and insomnia due to symptoms of PD

Some nonpharmacological strategies include:

- Having a hot bath before bedtime, which may shorten sleep-onset time by inducing sleep during the cooling phase
- Light bedtime snacks may alleviate symptoms of night-time hunger
- Avoiding fluid intake in the evening may reduce nocturia
- Relaxation techniques may help reduce stress and muscle tension

Subtle changes in PD medication regimens may result in major benefits in nocturnal sleep quality and subsequent daytime alertness. Strategies to improve nocturnal motor symptoms may worsen insomnia or induce vivid dreams. There often needs to be a degree of trial and error, and patients should be counselled regarding this. Targeting the individual's most troublesome symptoms is most likely to result in the best improvements in QoL.

Bedtime dosing of sustained-release levodopa preparations can help in reducing early morning PD symptoms, e.g., dystonia[87] and the addition of a catechol-O-methyltransferase inhibitor (COMT-I), such as entacapone or tolcapone, to the bedtime dose of levodopa can prolong its effect.[88] Alternatively, a nocturnal (on wakening) use of standard formulation or sustained-release levodopa may be helpful.

Table 4
Good sleep hygiene.

Avoid daytime napping
Increase daytime exercise
Avoid alcohol, caffeine, and tobacco
Avoid heavy meals or excessive liquid late in the day
Go to bed only when sleepy
Go to bed to sleep, not to read or watch television
Try to maintain a regular sleep pattern
If unable to sleep, get up and engage in relaxing activity, i.e., reading a book, and then return to bed when drowsy

Table 5
Potential pharmacologic treatments for sleep disturbances in Parkinson disease.

Symptom	Pharmacologic treatment
"Off" symptoms	Prolonged release levodopa Rotigotine patch
Dystonia	Prolonged release levodopa Rotigotine patch
Akathisia	Clozapine[89]
Restless legs syndrome	Reduce antidepressants
Periodic limb movements of sleep	Ropinirole Pramipexole Iron
Rapid eye movement sleep behavior disorder	Clonazepam Melatonin
Insomnia	Melatonin Quetiapine Benzodiazepines/zolpidem Sedating antihistamines
Excessive daytime somnolence	Reduce dopaminergic drugs, antihistamines, and hypnotics Modafinil Methylphenidate
Sleep attacks	Review non-ergot dopamine agonists
Depression	Antidepressants
Overactive bladder	Antimuscarinics
Obstructive sleep apnea	Review sedative medication Continuous positive airways pressure

Nocturnal symptoms may also benefit from the judicious use of a DA. In the RECOVER trial, transdermal rotigotine showed statistical improvement in almost all domains of PDSS-2: sleep-onset insomnia, early morning tiredness, nocturnal restlessness of limbs, early morning dystonia, early morning tremors, limb pain, muscle cramps, and breathing problems.[90] In EASE-PD, addition of prolonged release ropinirole to levodopa improved sleep as evidenced by change in baseline PDSS score.[91] A post-hoc subgroup analysis of EASE-PD showed improvements in early morning motor symptoms and global quality of sleep in those with PDSS scores ≤ 100 and in global quality of sleep for those with PDSS scores > 100.[92] The subgroup of PDSS with scores ≤ 100 have troublesome nocturnal symptoms in the form of greater daily awake 'off' time, reduced night-time sleep, and worse QoL compared with those with PDSS scores > 100. The CLinical Efficacy Of Pramipexole And Transdermal Rotigotine in Advanced Parkinson's Disease (CLEOPATRA-PD) study showed equal benefit of pramipexole or transdermal rotigotine over placebo.[93]

The hypnosedative zolpidem may be useful both for its sedative (insomnia) and muscle relaxing effects (insomnia and motor problems of PD).[94]

Melatonin (3 mg at night) has been shown to improve subjective sleep quality in a number of PD patients although there was no change in objective measures using PSG.[95]

Deep brain stimulation (DBS) of the subthalamic nuclei (STN) helps improve motor symptoms and sleep architecture (increased total sleep time and improved sleep maintenance) in PD,[96] but would not be recommended purely for this purpose.

6.1.2. Sleep fragmentation due to obstructive sleep apnea

Although CPAP is the most effective treatment for OSA, there are no data specific for its use in patients with PD.

6.1.3. Sleep fragmentation due to RLS and PLMS

Some nonpharmacological measures include:

- Good sleep hygiene
- Avoidance of alcohol, tobacco and caffeine
- Avoidance of drugs that exacerbate RLS: serotonergic and tricyclic antidepressants, antihistamines, and dopamine-receptor antagonists
- Correction of iron deficiency: iron replacement has been effective in reduction of RLS symptoms in non-Parkinsonian patients[97] and, hence, should be considered if ferritin levels are low. Although controlled trials are lacking, oral iron as ferrous sulphate concomitantly with vitamin C for absorption of food may be tried.[98] The cause of iron deficiency will need to be ascertained

The drug of choice for RLS and PLMS is a DA (pramipexole, ropinirole, or rotigotine).[99] When a DA cannot be used, e.g., the cognitively impaired or produces untoward effects, e.g., orthostatic hypotension, then alternatives include opiates, anticonvulsants (gabapentin), and benzodiazepines.[100]

6.1.4. REMSBD

Where REMSBD manifests as aggressive and/or violent behavior, environmental adjustment should be considered to protect the patient and his or her bed partner,[98] e.g., padding the floor, using raised padded bed rails, and sleeping in different rooms.

Low-dose clonazepam (0.5–1.0 mg), at night has been reported to improve REMSBD in 80%–90% patients[101] but controlled trials are lacking. Higher doses of clonazepam may run the risk of adverse effects of nocturnal confusion, daytime sleepiness, and worsening of OSA (if present).

Melatonin may improve REMSBD in doses up to 12 mg at night[102]; adverse effects include morning headaches, morning drowsiness, and delusions or hallucinations. Symptomatic improvement of REMSBD in PD patients has also been reported with pramipexole.[103] A small case series reported improvement of REMSBD with donepezil.[104]

6.1.5. Depression

Depression and anxiety may respond to improvements in motor symptoms due to adjustments in dopaminergic therapy. Pramipexole has also been shown to be of similar antidepressant activity as fluoxetine[105] better than sertraline[106] in improving mood when used as an adjunct to levodopa. This may be a class effect of DAs at the limbic dopamine D3 receptors, as both pramipexole and pergolide showed comparable benefits in MADRS scores.[107] In the EASE-PD Adjunct Study, prolonged-release ropinirole also improved mood as assessed by the Beck Depression Inventory.[91]

The evidence base for choosing an antidepressant in PD is poor and so no particular antidepressant can be recommended over another.[108,109] However, it is perhaps worth noting that bupropion and sertraline appear to inhibit dopamine reuptake[21,110] and so, theoretically may benefit motor symptoms as well as mood.

6.1.6. Nocturnal hallucinations/vivid dreams

Symptomatic improvement may be achieved by reduction (or removal) of evening doses of antiparkinsonian medications. Occasionally, atypical neuroleptics may be necessary; adverse events may be avoided by starting at low doses and gradually titrating up to the effective dose for that individual. Clozapine has been shown to reduce psychosis, anxiety, and hypersexuality in patients with PD.[111] However, use is limited by a need to regularly monitor blood count and prescribing being limited (in many parts of the United Kingdom) to consultant psychiatrists. Quetiapine is the drug of choice in clinical practice at a starting dose of 12.5–25 mg.

6.1.7. Nocturia

Some nonpharmacological measures to reduce nocturia include:

- Good sleep hygiene
- Avoidance of caffeine, alcohol
- Bladder training: voiding of urine before sleeping

- Reduction of fluid intake beyond the evening
- Bedside commode, pads, or conveen sheath urinal

Overactive bladder syndrome may benefit from drugs with antimuscarinic properties, such as tolterodine, oxybutynin, and solifenacin, but these drugs have the potential to cause or worsen confusion. If nonpharmacological and pharmacological measures fail, then botulinum toxin may be beneficial.[112]

Prostatism is a common comorbidity and may indicate a need for urodynamic studies if obstructive symptoms are significant.

6.2. EDS

Some nonpharmacological measures to reduce EDS include:

- Good sleep hygiene
- Avoiding sedentary activities and participating in external activities (day centers) may provide stimulation
- Avoid driving due to increased risk of vehicle accidents during periods of "sleep attacks"
- Physical exercise appropriate to level of functioning may help increase daytime wakefulness; avoidance of strenuous exercise for 3–4 hours prior to sleep

It may be necessary to reduce the dose or stop using DAs completely.[85] EDS may worsen with all dopaminergic therapy but is more marked with DAs than levodopa. In more severe cases of EDS, e.g., where the individual is falling asleep during meals or mid-conversation, then the stimulant modafinil may be of benefit, although the trial evidence is conflicting.[113,114] Methylphenidate may be worth trying, when all other options fail.[115] Caffeine (an adenosine A2A receptor antagonist) may be a more affordable alternative, albeit with no evidence base for its use in EDS.

7. Conclusion

Sleep disturbances are common in patients with PD and their sleep partners, but they are often overlooked by an emphasis on the motor manifestations of PD. The presence and cause(s) of sleep disturbances need to be identified as appropriate management can significantly improve the QoL of the person with PD and his or her caregiver. A number of assessment tools have been developed to aid in the detection and management of sleep problems in patients with PD.

It is imperative upon all healthcare professionals dealing with patients with PD to update them and gain experience in the diagnosis and management of these conditions. Although the evidence base is weak, all patients with PD will potentially benefit from advice on good sleep hygiene, while more specific pharmacological therapies will need to be tailored to each individual's sleep problem(s). Patients and caregivers should be warned of the potential limitations of therapeutic interventions and treatment should be targeted at their most troublesome symptoms.

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