

# Sleep disorders in Parkinson's disease

Israt Jahan<sup>1</sup>  
Robert A Hauser<sup>2</sup>  
Kelly L Sullivan<sup>1</sup>  
Amber Miller<sup>1</sup>  
Theresa A Zesiewicz<sup>1</sup>

<sup>1</sup>Department of Neurology,  
Parkinson's Research Foundation,  
<sup>2</sup>Departments of Neurology,  
Molecular Pharmacology, and  
Physiology, University of South  
Florida, Parkinson's Disease  
and Movement Disorders Center,  
Tampa, FL, USA

**Abstract:** Sleep disorders occur commonly in Parkinson's disease (PD), and reduce quality of life. Sleep-related problems in PD include insomnia, restless legs syndrome, rapid eye movement sleep behavior disorder, sleep apnea, parasomnias, excessive daytime sleepiness, and sleep attacks. This article reviews sleep disorders and their treatment in PD.

**Keywords:** insomnia, restless legs syndrome, sleep apnea

## Introduction

Sleep disorders occur commonly in Parkinson's disease (PD), and were initially noted by James Parkinson in his original monograph. Recent estimates place the prevalence of sleep disturbance in PD at almost 100%.<sup>1,2</sup> Sleep-related problems in PD can be divided into disturbances of sleep and wakefulness. Disturbances of sleep include insomnia, restless legs syndrome, rapid eye movement (REM) sleep behavior disorder, sleep apnea, and parasomnias. Disturbances of wakefulness include excessive daytime sleepiness (EDS) and sleep attacks. Sleep disorders are a major cause of disability in PD patients, and may have a substantial impact on quality of life. This review will focus on the etiology and treatment of sleep disorders in PD.

## Somnolence and excessive daytime sleepiness

Somnolence and EDS occur commonly in PD. Etiologies of somnolence in PD include reversal of the sleep-wake cycle, the disease process itself, disrupted sleep due to a variety of motor and nonmotor causes, and the use of dopamine agonists and other antiparkinsonian medications. Several studies have found that dopamine agonists are more likely to cause somnolence than levodopa. The soporific effects of the commonly used dopamine agonists appear to be similar as assessed by Epworth Sleepiness Scale (ESS) scores.<sup>3-6</sup>

The use of pramipexole as monotherapy in mild to moderate PD was found to cause somnolence in 18% of pramipexole-treated patients compared to roughly 9% of placebo-treated patients.<sup>7</sup> In a five-year study comparing ropinirole and levodopa as initial therapy, the incidence of somnolence was approximately 27% in ropinirole-treated patients and 19% in levodopa-treated patients. Another randomized placebo-controlled trial assessing the efficacy and safety of ropinirole in treating early PD found that somnolence occurred in 36% of ropinirole-treated patients compared to approximately 5% of patients taking placebo.<sup>8</sup> Somnolence that is caused by dopamine agonists may be dose related, but may also emerge or worsen after a

Correspondence: Israt Jahan  
Department of Neurology, University  
of South Florida, 12901 Bruce B Downs  
Florida, Tampa, FL 33612, USA  
Tel +1 813 974 5909  
Fax +1 813 974 8032  
Email mita\_fl@yahoo.com

period of time on a stable dose. In a retrospective review of clinical trial data, Hauser and colleagues found that early PD patients experienced the onset of worst reported somnolence  $10 \pm 1.5$  months (range 0.03–22 months) after starting pramipexole and after  $6.7 \pm 1.5$  months at their maximum dose.<sup>9</sup>

EDS occurs in PD patients, and is usually associated with dopamine agonist use. EDS may occur with use of other PD medications, including levodopa/carbidopa. However, EDS as measured by the ESS does not always correspond to shortened sleep latency as quantified by the Multiple Sleep Latency Test (MSLT).<sup>10</sup> In addition, nocturnal sleep disturbance as measured by polysomnogram (PSG) may not account for the “severity” of daytime sleepiness in PD patients with EDS.<sup>10</sup>

Treatment of EDS warrants a review of all medications, and elimination of possible offending agents when feasible. Nonantiparkinsonian medications that are associated with sleepiness such as benzodiazepines should be reduced and discontinued. If EDS developed during or shortly after the introduction of an antiparkinsonian medication, that medication should be reduced if possible, and discontinued. Patients with EDS that does not resolve with medication changes should undergo an overnight sleep PSG to exclude the presence of a treatable sleep disorder such as sleep apnea.

Several studies have assessed the therapeutic effectiveness of modafinil, a medication that is US Food and Drug Administration (FDA)-approved to treat narcolepsy, in the treatment of EDS in patients with PD.<sup>11–13</sup> Two studies found that modafinil improved EDS on a subjective level using the ESS,<sup>12,13</sup> while a third study reported some subjective, but nonsignificant, improvements using the ESS.<sup>11</sup> However, there was no objective improvement in EDS as measured by the MSLT in two studies that found objective improvement.<sup>11,13</sup> The possible ramifications of this are concerning if patients subjectively feel that their EDS is improved enough to drive, for example, but may, in fact, still suffer from EDS. Dextroamphetamine and methamphetamine may improve EDS, but have high abuse potential and should be used with caution. Pemoline, another stimulant, is associated with potential hepatotoxicity. Additional side effects of stimulants include headaches, irritability, nervousness, tremulousness, insomnia, anorexia, gastrointestinal disturbances, and palpitations.<sup>14</sup>

The issue of driving safety should be discussed with all PD patients and caregivers, particularly those patients who suffer from EDS or somnolence. Patients should be informed

that sleepiness is common in PD and may be associated with the disease itself, or caused by sleep disorders or medications. Because EDS and somnolence may occur during the initial titration of dopaminergic medications, particularly dopamine agonists, patients should be started on the lowest doses of these medications possible. Patients should be routinely asked about EDS during visits. Those patients who do suffer from substantial EDS and who doze off with little or no warning should not drive.

## Sleep attacks (unintended sleep episodes)

A “sleep attack” describes “an event of overwhelming sleepiness that occurs without warning, or with a prodrome that is sufficiently short or overpowering to prevent the patient from taking appropriate protective measures”.<sup>15</sup> The term “sleep attack” re-emerged in 1999 when Frucht and colleagues described sudden episodes of falling asleep that caused driving accidents.<sup>15</sup> Several experts have suggested that the term “unintended sleep episodes (USE)” is a more appropriate description of these events, arguing that the word “attack” fails to recognize the background of sedation that may precede the onset of sleep.<sup>16,17</sup> Patients experiencing “sleep attacks” may fall asleep because they are continuously sleepy, and then fall asleep in situations where resistance to sleep is decreased.<sup>18</sup> However, patients may suffer from discreet waves of irresistible sleepiness that occur against a perceived background of normal wakefulness.<sup>19</sup> When prodromes of sleepiness occur, they are often marked by yawning, blinking, or tearing.

One prospective survey of 236 PD patients found that 72 (30.5%) reported sudden sleep episodes.<sup>20</sup> Another study that used structured telephone interviews in 2,952 PD patients in two German counties found that 177 (6%) patients had “sleep attacks”.<sup>21</sup> Ninety-one patients had at least one sleep attack without a warning sign, while 86 patients always had a warning sign prior to a sleep attack. Seventy-five percent of patients who experienced “sleep attacks” had an ESS score of greater than 10, while 37% of patients had an ESS score of greater than 15.

“Sleep attacks” may be caused by antiparkinsonian medications, usually dopamine agonists. One retrospective review of sleep attacks or narcoleptic-like events in PD found that these events occurred in 6.6% of patients taking dopamine agonists.<sup>22</sup> The package insert for pramipexole in the United States recommends that patients must be informed that they should not drive a vehicle or engage in potentially dangerous activities until they have enough experience to gauge whether

pramipexole adversely affects their mental performance.<sup>23</sup> “Sleep attacks” may also occur with other antiparkinsonian medications, including levodopa and entacapone.

Motor vehicle accidents and “sleep attacks” were first reported by Frucht and colleagues in a case series.<sup>15</sup> Frucht and colleagues later determined that of approximately 400 PD patients who took pramipexole at three New York centers, there was an annual incidence of sleep attacks causing automobile accidents of 2%.<sup>24</sup> Hauser and colleagues conducted a retrospective chart review of 37 PD patients who participated in pramipexole clinical trials.<sup>25</sup> Using structured interviews with patients who reported moderate to severe somnolence, the yearly automobile accident rate due to falling asleep was calculated to be 1.6%. Hobson and colleagues found that of 638 PD patients, almost 4% of patients reported experiencing at least one episode of sudden sleep while driving after they were diagnosed with PD.<sup>26</sup> Another study by Ondo and colleagues found that almost 23% of patients reported falling asleep at the wheel.<sup>27</sup> Falling asleep while driving is associated with older age (odds ratio [OR] = 0.96, 95% confidence interval [CI]: 0.93 to 0.99;  $P = 0.003$ ), use of levodopa (OR = 2.96, 95% CI: 1.21 to 7.24;  $P = 0.018$ ), and use of any dopamine agonist (OR = 3.08, 95% CI: 1.47 to 6.42;  $P = 0.003$ ). Brodsky and colleagues questioned 101 consecutive PD patients and 100 non-PD age-matched controls about sleep habits and falling asleep while driving.<sup>28</sup> Almost 21% of PD drivers experienced sleep episodes, compared to 6% of controls ( $P < 0.05$ ). PD drivers who experienced a sleep episode while driving had greater ESS scores than patients who did not fall asleep at the wheel (ESS  $11.62 \pm 6.4$  vs.  $8.4 \pm 4.1$ ;  $P = 0.05$ ).

## Insomnia and Parkinson's disease

Insomnia is a common complaint in patients with PD.<sup>29</sup> It appears to fluctuate over time in individual patients.<sup>30</sup> Insomnia in PD may occur as a direct consequence of the disease process itself<sup>31</sup> or it may be secondary to factors associated with the condition, such as painful dystonia, nighttime reemergence of tremor, mood disturbances, and effects of medications, or nocturia.<sup>32–36</sup> Insomnia in PD has also been associated with worse Montgomery–Asberg Depression Rating Scale scores and female sex.<sup>37</sup> Disturbed sleep can have a significant impact on patients' cognitive and physical function and may be associated with distress and depression. Insomnia also impacts patients' and caregivers' quality of life.<sup>38</sup>

Treatment of insomnia in PD patients first requires identifying its underlying causes. Interventions include

adding levodopa/carbidopa or a dopamine agonist before bedtime if patients are awakened by painful dystonia, as well as treatment of urinary incontinence or discontinuing medications that contribute to insomnia.

Several controlled trials have evaluated the use of conventional sleeping aids as treatment for insomnia in PD. One study that evaluated the effect of levodopa/carbidopa on insomnia in PD found that when a sleep medication was administered at bedtime, sleep quality was improved from 67% to 93% using a visual analog scale as well as early morning waking as measured by bed actigraphy.<sup>39</sup> A second study looking at the use of levodopa/carbidopa slow release (SR) found that it did not improve the number of hours slept, number of awakenings, sleep latency, or general sleep satisfaction.<sup>40</sup> However, there was a significant improvement in mean nocturnal akinesia score in the levodopa-treated group compared to the placebo group.

Melatonin, a hormone produced by the pineal gland, functions in regulating the circadian cycle by causing drowsiness.<sup>41</sup> A study that measured nocturnal sleep by actigraphy, sleep diaries, and the ESS found that melatonin had a small benefit in treating insomnia in doses of 5 mg and 50 mg, with total sleep time improving by 10 minutes (from 5 hours 13 minutes to 5 hours 23 minutes; 3%) with the 50 mg dose of melatonin.<sup>42</sup> However, another study found that melatonin 3 mg improved sleep quality by subjective, but not objective, measures (ie, PSG).<sup>43</sup>

Deep brain stimulation (DBS) is used to treat the symptoms of PD. Several studies using PSG found an improvement in sleep quality following DBS of the subthalamic nucleus.<sup>44–46</sup> However, DBS is not used primarily as a treatment for insomnia in PD.

## Restless leg syndrome and Parkinson's disease

Restless legs syndrome (RLS) is a neurological disorder characterized by an uncontrollable urge to move the legs, often related to unpleasant sensations in the legs while at rest. It occurs most often in the evening, and typically improves when moving the legs. Patient use various terms to describe the sensations of RLS, including “burning, creeping, crawling, or itching”. Estimates of the prevalence of RLS in PD patients have ranged from 3% to 20%.<sup>47</sup> PD patients with RLS appear to have a longer duration of PD symptoms, more severe PD disability, a greater degree of cognitive dysfunction, and a longer duration of antiparkinsonian therapy than those without RLS.<sup>48</sup> In one study, the most significant factor associated with the development

of RLS in PD was the duration of antiparkinsonian therapy.<sup>48</sup>

Functional imaging studies suggest reduced dopaminergic function in the striatum in both RLS and PD.<sup>49,50</sup> The etiological relationship between PD and RLS remains unclear. While the dopamine agonists ropinirole and pramipexole are FDA-approved to treat moderate-to-severe primary RLS there are currently no controlled trials in PD patients with RLS. In non-PD patients, a single dose of pramipexole of between 0.125 and 0.750 mg that is ingested two to three hours before bedtime may adequately control sensory symptoms and motor signs of RLS.<sup>51</sup> Clinical trials indicate that approximately 1.5 to 2 mg of ropinirole ingested before bedtime is effective in relieving symptoms of RLS, although doses in the trials ranged from 0.25–4.0 mg once daily.<sup>52</sup> Rotigotine (Neupro) is another nonergoline dopamine agonist with selectivity for D1, D2, and D3 receptors that is administered by 24-hour transdermal patches. Rotigotine was under review by the FDA as treatment for RLS prior to it being withdrawn from the market due to crystallization.

## REM sleep behavior disorder

REM sleep behavior disorder (RBD) is a type of parasomnia in which patients “act out” dramatic or violent dreams during the REM sleep stage. Nighttime behaviors for RBD patients include screaming, kicking, punching, or even injuring a bed partner. Recent evidence indicates that RBD may be a predictor of PD, as more than half of people who suffer from RBD may develop PD or parkinsonism within 12 years following their diagnosis, and almost an 18% will develop a neurodegenerative disease within five years of diagnosis.<sup>53</sup> In another study of 36 PD patients, the presence of RBD in PD was strongly associated with symptoms and signs of orthostatic hypotension (systolic blood pressure lying to standing =  $-25.7 \pm 13.0$  mmHg vs  $-4.9 \pm 14.1$  mmHg,  $P < 0.001$ ; and orthostatic symptom prevalence = 71% vs 27%,  $P = 0.0076$ ).<sup>54</sup> RBD in PD occurs more commonly in patients suffering from the nontremor-predominant subtype of the disease.<sup>55</sup> One study found that cognitive impairment in PD patients is closely related to the presence of REM sleep behavior disorder.<sup>56</sup>

## Sleep apnea

Sleep apnea is a sleep disorder that is characterized by repetitive pauses in breathing during sleep that last long enough so that one or more breaths are missed. Central sleep

apnea has been found to occur in neurodegenerative diseases including PD.

PD patients have an increased rate of snoring compared to controls, and some studies estimate that 20% of PD patients may suffer from sleep apnea despite normal body mass index.<sup>57</sup> One case control study of 21 PD patients found that 20% had mild sleep apnea, while 23% had moderate to severe sleep apnea. Another study using polysomnographic evaluations also found a greater incidence of obstructive sleep apnea in PD patients compared to age-matched controls.<sup>58</sup> However, another study evaluated 100 PD patients (50 unselected, consecutive patients matched for age, sex and body mass index and 50 patients referred for sleepiness) and 50 in-hospital controls. Subjects underwent a video-polysomnography, and sleep apnea was found to be less frequent in the PD group (27% patients, including 6% with mild, 11% with moderate and 10% with severe sleep apnea) than in the in-hospital control group (40%,  $P < 0.002$ ). Sleep apnea in PD patients was not associated with increased sleepiness, nocturia, depression, cognitive impairment, or cardiovascular events. However, sleep apnea as more frequently identified and severe in the most disabled patients. Patients with PD did not display sleep hypoventilation, stridor or central sleep apnea. The authors concluded that obstructive sleep apnea does not seem to be a clinically relevant issue in PD, and that daytime sleepiness, nocturia and cognitive impairment are mostly caused by other, nonapneic mechanisms.<sup>59</sup>

Treatment for sleep apnea includes oxygen use, weight loss, continuous positive airway pressure (CPAP), or bilevel positive airway pressure (BiPAP). Polysomnography may be used to determine the presence and baseline severity of sleep apnea, and may be repeated to determine the effectiveness of sleep apnea treatment. One study found that the use of modafinil used adjunctively with CPAP improved subjective daytime sleepiness in PD patients suffering from sleep apnea compared to treatment with CPAP alone.<sup>60</sup>

## Conclusion

Sleep disorders occur commonly in PD patients, and significantly impair quality of life. Health care providers need to be cognizant of the frequency of sleep disorders in PD patients, and screen for these disorders during routine patient visits. The contribution of medications to sleep dysfunction in PD needs to be addressed at these visits, and patients may need further formal sleep evaluations if no etiology for sleep disruption is found. Further research is needed to evaluate the treatment of sleep disorders in PD.



## Disclosures

The authors report no conflicts of interest in this work.

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