Sleep disorders in Parkinson’s disease

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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%.1,2 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.3–6

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.7 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.8 Somnolence that is caused by dopamine agonists may be dose related, but may also emerge or worsen after a...
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”. The term “sleep attack” re-emerged in 1999 when Frucht and colleagues described sudden episodes of falling asleep that caused driving accidents. 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. Patients experiencing “sleep attacks” may fall asleep because they are continuously sleepy, and then fall asleep in situations where resistance to sleep is decreased. However, patients may suffer from discreet waves of irresistible sleepiness that occur against a perceived background of normal wakefulness. 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. Another study that used structured telephone interviews in 2,952 PD patients in two German counties found that 177 (6%) patients had “sleep attacks”. 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. 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
Insomnia and Parkinson’s disease

Insomnia is a common complaint in patients with PD. It appears to fluctuate over time in individual patients. Insomnia in PD may occur as a direct consequence of the disease process itself 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. Insomnia in PD has also been associated with worse Montgomery–Asberg Depression Rating Scale scores and female sex. 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.

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. 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. 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. 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. However, another study found that melatonin 3 mg improved sleep quality by subjective, but not objective, measures (ie, PSG).

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. 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%. 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 antiparkinson therapy than those without RLS. In one study, the most significant factor associated with the development
of RLS in PD was the duration of antiparkinsonian therapy.48

Functional imaging studies suggest reduced dopaminergic function in the striatum in both RLS and PD.49,50 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.51 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.52 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.53 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 ± 13.0 mmHg vs –4.9 ± 14.1 mmHg, P < 0.001; and orthostatic symptom prevalence = 71% vs 27%, P = 0.0076).54 RBD in PD occurs more commonly in patients suffering from the nontremor-predominant subtype of the disease.55 One study found that cognitive impairment in PD patients is closely related to the presence of REM sleep behavior disorder.56

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.57 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.58 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.59

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.60

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.

References