

Sleepiness

in Parkinson Disease



BY: TANYA SIMUNI, MD

Associate Professor of Neurology, Director of Parkinson's Disease and Movement Disorders Center
Northwestern University
NPF Center of Excellence
Chicago, IL



Excessive daytime sleepiness (EDS), while frequently seen with increasing age in the general population (perhaps due to changes in sleep architecture and regulation of the sleep-wake cycle) can be more pronounced and disabling in people with Parkinson disease (PWP). Significant EDS is present in 15%–20% of PWP compared with 1% of healthy elderly individuals. The rate of EDS in PWP increases with the duration of their illness. The reasons for EDS in PD involve many factors that include the effects of PD motor disability, the disease process, impaired nocturnal sleep, the impact of dopaminergic medications, and co-existing conditions such as depression and dementia. This article will briefly review the mechanisms that are important in development of EDS in PD, and it will also address practical measures for improvement.

The Role of Dopamine in the Sleep-Wake Cycle

PD is characterized by loss of dopaminergic cells in the nigrostriatal pathways (deep pathways located in the bottom of the brain) that result in the alteration of normal function of a group of brain circuits important in PD. These brain circuits are referred to collectively as the basal ganglia. Normal sleep consists of cycles of slow wave sleep (non-REM) that then transitions through stages of lighter (stage I), followed by deeper sleep (stage IV), and then finally rapid eye movement sleep (REM). Non-REM sleep normally constitutes approximately 75% of sleep. REM therefore accounts for about 25% of the remaining sleep and it will occur usually in the morning hours. REM sleep is the portion of sleep associated with dreams. Traditionally, dopamine was not considered to be one of the neurotransmitters involved in the regulation of the sleep-wake cycle. However, more recent data has demonstrated a role of dopamine in the regulation of REM and non-REM sleep, potentially via modulation of basal ganglia structures and include an influence on the firing pattern of the subthalamic and pedunculopontine nuclei. These nuclei belong to the reticuloactivating system (RAS) which are areas responsible for the maintenance of alertness and arousal. Clinically, a dopaminergic deficit has been closely linked to sleep disorders. In the animal model of parkinsonism (MPTP model), dopamine depletion has resulted in daytime sleepiness and

sudden onset REM sleep, which is considered to be an electrophysiological correlate of a narcolepsy-like phenomenon. Narcolepsy is a condition associated with sudden onset sleep attacks. Although the underlying causes remain unknown, it is hypothesized that this phenomenon can be traced to the effect of dopamine loss on neural activity on several substrates. One such substrate that has been found to regulate wakefulness is orexin-A, or hypocretin-1—a neuropeptide produced in the hypothalamus. Orexin-A deficiency has been identified as a cause of somnolence in narcolepsy. The role of orexin in PD-related somnolence remains unknown. Studies have demonstrated decreased orexin levels in the cerebrospinal fluid of PD patients correlates with the severity of the disease. It should be noted, however, that other groups have not found a correlation of orexin with EDS in PD.

Impact of Poor Night's Sleep on Daytime Somnolence in Parkinson Disease

Sleep dysfunction has been recognized as an intrinsic part of PD even dating back to the original 1817 description of paralysis agitans by James Parkinson. Reported prevalence (frequency) rates have ranged from 75% to 98% in PWP. Nocturnal sleep disorders in PD can be

classified into disorders of sleep initiation and maintenance, and parasomnias. Both of these problems can contribute to EDS.

Disorders of sleep initiation and maintenance, which can be characterized by symptoms such as difficulty falling asleep, poor quality sleep, frequent nighttime awakenings, and early arousal, are common in the elderly. These symptoms however, are even more common in PWP. The length of nocturnal sleep seems to reduce with aging, and the number of arousals paradoxically increases. Daytime naps become more common and older people tend to go to bed earlier and arise earlier. Electrophysiologically, this type of sleep disturbance is seen as a reduction in the deep stages of sleep, stages III and IV, while the percentage of REM sleep itself does not change. The latency (time until occurrence) to the first REM sleep episode decreases. These changes lead to decreased sleep efficiency (reduced amount of time spent sleeping out of the total time spent in bed).

In PWP, a variety of processes may interfere with sleep initiation and maintenance. Motor manifestations of PD, such as the inability to move in bed, stiffness, tremor, and cramps may disturb normal sleep. Primary sleep disorders such as restless legs syndrome (RLS), periodic limb movements in sleep (PLMS), and obstructive sleep apnea (OSA) have also been found to be more common in PWP than in the general population.

RLS is characterized by a sensation of motor restlessness that occurs at rest, predominantly in the evening. At night RLS improves with activity. RLS can interfere with the ability of the person to fall asleep.

PLMS is defined as the syndrome of repetitive, periodic highly stereotyped leg movements that occur in sleep and can cause awakenings. PLMS frequently accompanies RLS.

The frequency of RLS in the general population has been estimated to be 10%, though it remains under-diagnosed in the population. Based on the recent data, RLS is even more common in PWP and it affects 20% of the PD population. RLS can either precede or follow onset of PD, but is unlikely to be a preclinical marker. The cause of RLS is unknown, but it is associated with dopamine deficiency (at least based on the fact that medications used for the treatment of PD are highly effective for RLS symptoms).

Another common cause of sleep disturbance in aging people is obstructive sleep apnea (OSA), characterized by a blockage of the airway that leads to a cessation of breathing. This cessation of breathing can happen frequently at night, leading to arousals and consequently a decrease in sleep quality. OSA results in insufficient amounts of oxygen to the brain, and this results in frequent awakenings, daytime fatigue and headaches. The prevalence of OSA in the elderly American population is 2.5% to 4.4%, but has been reported to be up to 25% depending on the diagnostic criteria used to define the syndrome. OSA has been shown to be associated with PD (20% to 31% of patients), but the data of the direct relationship between these two conditions has been inconclusive.

The problems of sleep initiation and maintenance as well as daytime somnolence may be compounded further by other PD-related conditions such as depression, dementia, and autonomic symptoms. Depression is a common cause of sleep disturbance in the elderly. Difficulty with sleep initiation, frequent arousals and early morning wakefulness are the typical complaints in depression. Sleep dysfunction can be one of the earliest signs of mood dysfunction. Considering the prevalence of depression of 40% in PWP, it can be a significant contributing factor to an impaired nights' sleep in PD. Cognitive impairment can also contribute to impaired sleep in PD. Autonomic dysfunction is another common cause of the disrupted

sleep pattern in PWP. Increased urinary frequency at night (nocturia) occurs in 80% of PWP.

Parasomnias

The term parasomnia refers to a variety of sleep-related behavioral phenomena, including sleep walking (somnambulism), vivid nightmares, night terrors, and REM sleep behavior disorder (RBD). Hallucinations and nightmares affect almost 20% of PWP, and can contribute to sleep problems and EDS. They usually are provoked by PD medications but can occur as a result of infection, use of sedatives, electrolyte imbalance as well as other causes. Hallucinations and night dreams are more common with advanced disease and in patients with underlying cognitive impairment. It is important to distinguish between vivid nightmares and RBD because the cause and treatments differ. RBD is characterized by prominent motor activity associated with dreaming during REM sleep, plus harmful sleep behaviors, dreams that appear to be “acted out,” and/or actions that disrupt sleep continuity. The cause of violent behavior is related loss of muscle tone that normally accompanies REM sleep, and this results in people “acting out” their dreams. The syndrome has been found in up to 47% of PD patients referred for sleep evaluation. The diagnosis of RBD requires polysomnographic monitoring (sleep study) to demonstrate loss of muscle tone during REM sleep behavior. Furthermore, it is now recognized that RBD can be a pre-clinical marker of an evolving parkinsonian disorder, as evidenced by the observation that 38% of patients diagnosed with RBD developed a parkinsonian syndrome within approximately 4 years.

In conclusion, there are multiple factors that contribute to impaired sleep and disruption of the sleep-wake cycle in PD. Surprisingly, studies have failed to demonstrate direct correlation between the degree of daytime somnolence and the quality of night sleep. The factors that have been shown to correlate with the severity of EDS are the duration of PD, advanced stage of the disease, and drug treatment.

EPWORTH SLEEPINESS SCALE

Please answer the question: “How likely are you to doze or fall sleep in the following situations (in contrast to just feeling tired)? This refers to your usual present way of life. Even if you have not done some of these things recently, try to recall whether they may have occurred previously.” Please use the following scale to choose the most appropriate number for each situation: **0 = would never doze; 1 = slight chance of dozing; 2 = intermediate chance of dozing; 3 = high chance of dozing.**

Situation	Chance of event at present (score 0-3)
ESS	
1. Sitting and reading	
2. Watching television	
3. Sitting, inactive, in a public place (eg., theater or a meeting)	
4. As a passenger in a car for 1 hour without a break	
5. Lying down to rest in the afternoon when circumstances permit	
6. Sitting and talking to someone	
7. Sitting quietly after a lunch without alcohol	
8. In car when stopped in a few minutes for traffic	

Adapted from Johns, M. W. (1991). “A new method for measuring daytime sleepiness: the Epworth sleepiness scale.” *Sleep* 14(6): 540-5.



Impact of Parkinson Disease Medications on EDS

The impact of dopaminergic therapy on EDS in PD patients is complex. The ultimate effect of these agents is dependent on variables such as disease stage, presence of cognitive dysfunction, as well as type and dose of dopaminergic therapy. Based on the available data, most experts agree that sleepiness can be the side effect of treatment with either levodopa or dopamine agonists. Dopamine agonists are more prone to cause EDS compared to levodopa, for example, in randomized controlled studies somnolence occurred in 32.4% of patients treated with pramipexole (Mirapex®) versus 17.3% of those treated with levodopa, and in 27.4% treated with ropinirole (Requip®) versus 19.1% of levodopa treated patients, (though the difference was not statistically significant in the latter study). Studies seem to suggest that drug-induced somnolence is a “class effect” of all dopaminergic medications rather than a particular agent. Therefore, dopamine drugs seem to play a

key role in sleepiness. The factors that contribute to the risk of somnolence include advanced disease, age and presence of underlying cognitive dysfunction.

While EDS has been long recognized in PWP, the entity was largely neglected until the description of unpredictable episodes of falling asleep while driving. These episodes were labeled as sleep attacks or episodes of sudden onset sleep. Frucht and colleagues were the first to report the occurrence of unpredictable and unintended sleep attacks in PWP, which resulted in car accidents in 8 patients who had been treated with pramipexole or ropinirole. They defined “sleep attacks” as “events of overwhelming sleepiness that occur without warning or with a prodrome that was sufficiently short or overpowering to prevent the person from taking appropriate protective measures.” That report raised a major concern regarding driving privileges of PWP. Subsequent to the initial report, a number of studies have examined the prevalence of sleep attacks and EDS in PWP. One of the largest survey-based studies was conducted by the Canadian

Movement Disorders Group. The study enrolled 638 highly functional, cognitively intact PD patients, of whom 420 were current drivers. EDS and sleep attacks were assessed by the Epworth Sleep Scale (ESS), the self administered 8-item questionnaire which is widely used in the clinical practice to measure the person’s general level of daytime sleepiness. An ESS score of >10 was considered to be in the “sleepy” range. Overall, EDS was present in 51.3% (327/638) of the PD patients and, similarly, in 50.7% (213/420) of the drivers. However, the incidence of sleep attacks was fairly modest, occurring in 3.8% (16/638) of the patients; only 0.7% (3/16) of these patients had sleep events without warning signs. None of the patients had sleep attacks in the absence of EDS. The group concluded that EDS was a common finding in PWP, even in those who were independent and without dementia.

Sleep attacks are rare, but it is clear that unintended episodes of sleep can come on quickly, and PWP should be warned of these risks, especially if they drive. Even in the absence of sleep attacks, EDS

has been associated with a substantially reduced quality of life. Impaired alertness due to EDS may lead to problems related to concentration, memory, and mood. These have been linked to loss of employment, social embarrassment, and motor vehicle accidents.

In conclusion, EDS is common in PWP. The causes are many and variable. There is no single remedy to treat EDS, but there are measures to prevent and improve sleepiness in PWP. Some of the practical recommendations are listed below:

- Recognition and accurate diagnosis- PWP and their families should be educated on the increased risk of sleepiness in PD.
 - PWP can complete the ESS scale to assess their risk of EDS (Table I). A score of >10 warrants further investigation and consultation with the physician
- Improvement of the quality of night sleep
 - Regular bed time and waking time
 - Appropriate amount of time in bed (about 7.5 hours)
 - Reduce nap frequency
 - Bright light exposure during the day
 - Increase the amount of day-time activities
- Recognition and treatment of sleep related disorders
 - OSA- the diagnosis requires sleep study. Treatment includes CPAP mask, weight reduction and other strategies
 - Restless legs syndrome/ periodic limb movement disorder- usually can be effectively treated with the adjustment of PD medications
 - RBD- diagnosis is based on the history and confirmed by the sleep study. Treatment includes clonazepam or melatonin
 - Insomnia- sleep hygiene, cautious use of hypnotics
- Treatment of PD motor symptoms
 - Adjustment of PD medications to reduce nocturnal dystonia, rigidity, tremor, etc.
- Nocturnal hallucinations and nightmares
 - Adjustment of PD medications, avoidance of sedatives and other medications that can affect REM sleep, use of antipsychotics like quetiapine (Seroquel) or clozapine (Clozaril)
- Depression
 - Use of anti-depressants that have sedative effect to provide benefit for the mood control and insomnia
- Dementia
 - Use of cholinesterase inhibitors (rivastigmine, galantamine, donepezil)
- Nocturia
 - Urological evaluation, use of medications to reduce urinary frequency (oxybutinin, tolterodine, etc.)
- Management of PD medication-induced sedation
 - PWP should be aware of the risk of EDS with all dopaminergic medications. Notify your MD if EDS occurs
 - Use the lowest dose of PD medications that provide satisfactory control of the motor symptoms
 - Trial of switching from one dopamine agonist to another
- Altering medications for EDS
 - Should be used **ONLY** if other treatment strategies have been applied and were not effective
 - Modafinil (Provigil)
 - Stimulants **HAVE NOT** been shown to be effective in PD
- Assessment of driving privileges
 - PWP should be aware of the risk of sleep attacks
 - Avoid driving if any signs of EDS, consult with MD
 - Consider driving safety evaluation (performed by rehabilitation centers) ■



REFERENCES:

1. Adler CH, Thorpy MJ. *Neurology (Suppl)* 64:S12, 2005.
2. Arnulf I et al. *Neurology* 58:1019, 2002.
3. Boeve B et al. *Mov Disord* 16:622, 2001.
4. Dhawan V et al. *Age Ageing* 35:220, 2006.
5. Drouot X et al. *Neurology* 61:540, 2003.
6. Ferreira JJ et al. *Eur J Neurol* 13:209, 2006.
7. Frucht S et al. *Neurology* 52:1908, 1999.
8. Hobson DE et al. *JAMA* 287:455, 2002.
9. Holloway RG et al. *Arch Neurol* 61:1044, 2004.
10. Johns MW. *Sleep* 14:540, 1991.
11. Ondo WG et al. *Arch Neurol* 59:421, 2002.
12. Rascol OD et al. *N Engl J Med* 342:1484, 2000.
13. Rye DB, Jankovic J. *Neurology* 58:341, 2002.
14. Schenck CH et al. *Neurology* 46:388, 1996.
15. Simuni T. *Neurol Clin (Suppl)* 22:S107, 2004.