REVIEW ARTICLE

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Excessive Daytime Sleepiness and Unintended Sleep Episodes Associated with Parkinson's Disease

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ABSTRACT

This article looks at the issues of excessive daytime sleepiness and unintended sleep episodes in patients with Parkinson's disease (PD) and explores the reasons why patients might suffer from these symptoms, and what steps could be taken to manage them. During the last decade, understanding of sleep/wake regulation has increased. Several brainstem nuclei and their communication pathways in the ascending arousing system through the hypothalamus and thalamus to the cortex play key roles in sleep disorders. Insomnia is the most common sleep disorder in PD patients, and excessive daytime sleepiness is also common. Excessive daytime sleepiness affects up to 50% of PD patients and a growing body of research has established this sleep disturbance as a marker of preclinical and premotor PD. It is a frequent and highly persistent feature in PD, with multifactorial underlying pathophysiology. Both age and disease-related disturbances of sleep-wake regulation contribute to hypersomnia in PD. Treatment with dopamine agonists also contribute to excessive daytime sleepiness. Effective management of sleep disturbances and excessive daytime sleepiness can greatly improve the quality of life for patients with PD.

Sleep disturbances in the late stages of Parkinson's disease (PD) were recognized by James Parkinson[1] in his classic monograph noting that: "The sleep becomes much disturbed. The tremulous motions of the limbs occur during sleep, and augment until they awaken the patient, and frequently with much agitation and alarm.....and at the last, constant sleepiness, with slight delirium". The diagnosis of PD requires the identification of its cardinal features, which are motor symptoms. Diagnosis is impossible without them, but recognition of the importance of non-motor features has increased over the past years.[2] Non-motor features (which include autonomic nervous system dysfunction, disorders of cognition and mood, psychosis, pain, loss of smell, and fatigue) affect nearly all PD patients, appear early in the course of PD, and contribute to excessive daytime sleepiness (EDS). All of these symptoms have significant adverse effects on the quality of life (QoL) of both patients and caregivers and require proper identification and treatment.[3-7]

Clinical presentation of sleep disturbance

Sleep-related problems in PD can be divided into disturbances of sleep and disturbances of wakefulness. Disturbances of sleep include insomnia, restless leg syndrome (RLS), rapid eye movement sleep behavior disorder (RBD), sleep apnea, and parasomnias. Disturbances of wakefulness include EDS, and sleep attacks. With normal aging, there is disruption of normal sleep architecture and alterations in the normal circadian rhythm leading to impaired nocturnal sleep and EDS.[8,9] These problems are accentuated in PD patients, with 60% to 90% having some form of sleep disturbance, particularly in the advanced stages of the disease.[3,6,10-12]

Epidemiology of sleep disturbance in Parkison's disease

The prevalence of sleep disturbance in PD is difficult to ascertain due to the heterogeneity of patients and different criteria used to categorize sleep disturbances. There is paucity of data on the role of gender in sleep disturbances. Smith and colleagues,[13] studied 153 patients and their spouses, and reported that sleep disturbances occurred more frequently in females with PD (41%) than in men (25%). However, there was no sex difference for difficulty initiating sleep. Van Hilten and colleagues,[14] observed that female patients experienced more difficulty maintaining sleep (87.5%) and excessive dreaming (68.4%) than males (64% and 31.6%, respectively). Sleep dysfunction in PD usually manifests by difficulty

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in initiating sleep, fragmented sleep, reversal of the sleep cycle, and EDS.[15,16] EDS was assessed using the Epworth scale in 101 patients with PD and 100 age-matched controls.[17] EDS was detected in 76% of patients with PD compared to 47% of controls (p<0.050). Nearly a quarter (24%) of patients with PD had scores in the diagnostic range of narcolepsy, compared to only 5% of controls (p<0.001).

Sleep disturbances in PD are numerous and there may be different combinations.[6,14,18-23] The cause of the disturbances are multifactorial and may be related to aging, Parkinsonian motor dysfunction, dyskinesia, pain, nocturia, nightmares, dopaminergic and non-dopaminergic medications, cognitive impairment, and a variety of specific sleep disorders, including RLS, periodic limb movements of sleep (PLMS), RBD, and sleep apnea. Collectively, they contribute to the increase in daytime sleepiness frequently found in PD patients.[24] EDS and RBD may be harbingers of PD and other synucleinopathies, such as multiple system atrophy,[25] and thus already present in the premotor phase of the disease. It is also clear that dopaminergic medications and particularly dopamine agonists can have a complex effect on sleep. Sometimes these medications cause insomnia, and their sedative properties may contribute to daytime sleepiness.[17,26-30] In other situations, they improve the quality of sleep by improving nocturnal immobility.[31,32] Therefore, dopaminergic medications can either improve or worsen sleep in PD patients.

Neuroanatomy of sleep in Parkinson's disease

The anatomical basis of sleep disturbances in PD is not fully understood, but it likely involves degeneration of both dopaminergic and non-dopaminergic systems. Sleep disturbances are primarily due to the progressive disease process impairing thalamocortical arousal and affecting sleep-regulating centers in the brainstem. Secondary causes are nocturnal disease manifestations, and side effects of pharmacological treatment. Mesocorticolimbic dopamine neurons that project from the ventral tegmental area (VTA) targeting the thalamus, hippocampus, and cerebral cortex are thought to be involved in the arousal mechanism.[33] Dopamine plays a complex role in state control, specifically maintains the wake state, and regulates sleep homeostasis.[34] These dopamine-mediated arousal functions are independent from the nigrostriatal dopaminergic system. Subsequently, the responsible mesolimbic dopaminergic system may also degenerate later than the nigrostriatal system.[34]

Aetiology of sleep disturbance in Parkinson's disease

Non-dopaminergic neurons have also been implicated in sleep dysfunction in PD. Reduced levels of hypocretin in the cerebrospinal fluid are an established biomarker in narcolepsy, and PD patients show narcolepsy-like sudden onset sleeps during the daytime, suggesting similar hypocretin action in these patients. Braak and his colleagues[35] hypothesis of ascending brainstem degeneration proposes early disease involvement of several other non-dopaminergic brainstem nuclei, such as the cholinergic pedunculopontine nucleus (PPN), serotonergic tegmental area, nucleus magnocellularis, and noradrenergic locus cereleus (LC). Degeneration of neurons in these sleep-wake related pathways (the flip-flop switch), which are associated with thalamocortical arousal, could contribute to the development of sleep dysfunction in PD.[36] The PPN has attracted particular attention because it is intimately related to the anatomic control of sleep, and is thought to play a critical role in mediating inhibition of voluntary muscles during REM.[16,37] This hypothesis has propelled our understanding of sleep dysfunction in PD. Interestingly, direct evidence of a beneficial effect of a normally functioning PPN has been given by deep brain stimulation of this nucleus, confirming that PPN promotes REM sleep and plays a role in switching from one state to another. Thus, low-frequency stimulation of the PPN increases alertness and high-frequency stimulation induces non-rapid eye movement sleep (NREM) sleep, while sudden withdrawal of the stimulation elucidates REM sleep.[38-40]

Excessive daytime sleepiness

EDS is defined as a chronic state of inability to stay awake during the day. A score greater than 10 on the Epworth Sleepiness Scale (ESS), or a mean sleep latency less than eight minutes on the Multiple Sleep Latency Test (MSLT)[30,41,42] is considered inappropriate sleepiness during waking hours and has been under-recognized in PD. EDS was initially

considered a side effect of non-ergot dopamine D2-D3 agonists,[43] but it is not restricted to a specific class of dopaminomimetic agents and may have other causes. Because of the many potential problems that can interfere with nocturnal sleep in patients with PD and the tendency of dopaminergic medications to induce sedation, EDS is a common problem.[44,45]

Epidemiology

One study found no increase in the prevalence of EDS in untreated PD patients compared with an age-matched healthy control group. EDS was more frequent in treated patients, suggesting that either the progression of the disease, the treatment, or a combination of both, may be critical in the development of this symptom.[46] Another study found that progression of the disease, before initiation of dopaminergic treatment, was associated with increased sleepiness.[47] Polysomnographic recordings indicate that the average patient with PD obtains only four to five hours of documented sleep per night instead of the approximately eight hours that are normally required.[19,48] In one study, 76% of consecutive PD patients reported EDS, compared with 47% of age-matched controls ($p<0.050$) and 24% had sleep scores in the range of patients with narcolepsy, compared to only 5% of controls ($p<0.001$).[17] EDS is common in PD,[6,14] however, it is a multifaceted phenomenon not solely related to dopaminergic medication. Next to dopaminergics, disease severity, "wearing-off", and sleep disordered breathing have been shown to influence PD-related EDS.[41]

Putative biological markers

The notion of PD-related EDS is supported by the fact that magnetic resonance imaging (MRI) brain morphometry demonstrated that in PD patients EDS was related to atrophy of the medial cerebellar peduncle (PD with EDS (mean+SD) 16.08+0.93mm vs. PD without EDS 17.82+0.80mm; $p=0.010$), leading the authors to suggest the involvement of degeneration of the pontomedullary respiratory centers in the development of PD-linked EDS.[49] In one study,[14] no significant difference was found in the degeneration of the pontomedullary respiratory centers between PD patients (44.4%) and control patients (31%). The diurnal pattern was similar with a peak in the early afternoon. The authors concluded that no relationship existed between PD and EDS, and that EDS was probably a consequence of aging, as reported previously by Carskadon[50] and Morewitz.[51] EDS was noted in patients with Parkinsonian syndromes in early descriptions[52] and spontaneous dozing during the daytime occurred in nearly half of PD patients in one study.[6] However, EDS has only received increasing attention since the controversially discussed report of "sleep attacks" in PD patients on dopaminergic therapy. These case reports first involved patients taking non-ergoline dopamine agonists[43] and were subsequently supplemented by case reports for virtually all other dopamine agonists and levodopa.

Clinical presentation

Patients with EDS have a tendency to fall asleep in unintended situations. Typically, these occur in relatively benign situations that are conducive to falling asleep such as while watching television or reading. However, in extreme situations patients may fall asleep during a meal, while in conversation, and in potentially dangerous situations such as while driving. Previous studies reported sleepiness with varying frequencies (42%[14] and 49%[6]).

Diagnostic tools

To identify sleepiness in an individual patient, it may be necessary to use sleep questionnaires such as the Epworth Sleepiness Scale (ESS),[5] which do not rely on subjective estimates of sleepiness, but rather on a measure of the propensity of the patient to fall asleep. The ESS is a set of eight questions, quick and easy to use for the patient and carer, and does not require technical measurements or the involvement of a sleep laboratory. The ESS has been shown to correlate with more cumbersome, expensive, and time-consuming tests such as the Multiple Sleep Latency Test (MSLT) in patients with sleep apnea.[5] It is the sum of eight items that ask for ratings on the tendency to doze in a variety of situations. The ratings are scaled from zero (no chance of dozing) to three (high chance of dozing) for each item. Higher scores indicate greater sleepiness as indicated by a higher likelihood to fall asleep during daytime activities. The ESS has been translated into different languages throughout the world. A validated Arabic ESS questionnaire was just as good as its English counterpart.[53]

The importance of addressing EDS in PD was highlighted by a report of eight patients who

suddenly fell asleep while driving a motor vehicle.[43] These episodes were termed "sleep attacks" by the author because they seemed to have occurred without warning, and were attributed to dopamine agonists because they disappeared when the drugs were withdrawn. This report generated intense interest in the nature and frequency of sleep disturbances in PD and a debate as to how these episodes are related to the use of dopamine agonists. It is generally thought that EDS in PD patients results from impaired nocturnal sleep. However, not all studies confirm this concept. The FAST TRACK study evaluated daytime sleepiness using the MSLT. In 27 PD patients, the MSLT scores did not correlate with the quantity and quality of the previous night's sleep or other sleep architecture measures, such as sleep stage percentage, and total sleep time.[54] Similarly, in another study, no correlation was found between MSLT score and total sleep time, sleep efficiency, arousal index, apnea-hypopnea, or periodic leg movement indices.[55] These studies suggest that the quality of nighttime sleep may not be the only factor responsible for daytime sleepiness. Whatever the mechanism, EDS (defined as being sleepy most of the day) is present in a large number of PD patients. Varying estimates have been reported, ranging from 15% to 75%.[17,56-63] The most widely used tools are the ESS, MSLT, Scales for Outcomes in PD (SCOPA-SLEEP), Parkinson's Disease Sleep Scale (PDSS), and Polysomnography (PSG). The possibility that dopaminergic medications, and especially dopamine agonists, may aggravate EDS has attracted considerable attention, again driven by the observation by Frucht and colleagues[43] that all patients who fell asleep while driving were receiving high doses of dopamine agonists. PSG studies have similarly demonstrated that total dopaminergic dose, rather than the specific dopaminergic agent, was the best predictor of EDS, as MSLT scores of patients on different dopaminergic therapies were similar to one another.[55] EDS may occur with use of other PD medications, including levodopa and carbidopa. Seventy percent of dysautonomic patients with PD reported sleep attacks compared to 17.8% of nondysautonomic patients with PD.[29]

Sleep attacks (unintended sleep episodes)

A sleep attack is described as "an event of overwhelming sleepiness that occurs without warning or with a prodrome that is sufficiently short or overpowered to prevent the patient from taking appropriate protective measure".[43] Others have suggested that sleep attacks in PD patients are more likely to represent an extreme form of EDS due to the combination of a sleep disturbance and the sedative effects of dopaminergic medication.[28] Sleep attacks in which patients fall asleep without an antecedent warning of sleepiness are not known to occur either physiologically or in association with pathologic conditions.[5] For this reason, the concept of a sleep attack has been abandoned even in narcolepsy.[64] It was proposed that sleep attacks represent an extreme form of sedation in patients who were sleep deprived and on sedative medications, and would be better termed unintended sleep episodes (USE). The term sleep attack re-emerged in 1999 when Frucht et al,[43] described sudden episodes of falling asleep that caused driving accidents. Some experts have suggested that the term 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.[28,65] Patients experiencing sleep attacks may fall asleep because they are continuously sleepy, and fall asleep in situations where resistance to sleep is decreased.[66] The concept of a sleep attack implies that the events are inevitable and occur without any warning whatsoever. The notion of USE implies that at-risk individuals can be identified and the episodes prevented by instituting appropriate treatment measures. Prodromes of sleepiness include yawning, blinking, or tearing.

Prevalence and risk factors

A prospective survey of 236 patients with PD found that 72 (30.5%) reported sudden sleep episodes.[29] Another study, which used structured telephone interviews in 2,952 patients with PD, found that 177 patients (6%) had sleep attacks.[67] 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. Although sleep attacks were initially described in patients receiving pramipexole and ropinirole, it is clear that sedative effects and USE can be seen with any dopaminergic agents, including levodopa,[68-71] and that these effects are dose related, occurring with greater frequency in patients taking relatively high doses. Thus, somnolence is more likely to occur in patients taking higher doses of dopaminergic medications

and is greatest when a given dose reaches its maximal concentration. The package insert for pramipexole in the US 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 determine whether pramipexole adversely affects their mental performance.[72] Sleep experts have criticized the term sleep attacks saying it is inappropriate as sleepiness is not adequately perceived, specifically in chronically sleepy patients, and electrophysiological signs of sleepiness precede sleep onset even in patients who are not aware of it.[73,74] This was confirmed when 47 somnolent PD patients underwent MSLT, and after each nap they were asked whether they had slept or dozed. Thirty-eight percent of the PD patients did not perceive at least one PSG-confirmed nap. These patients also showed a lower score on the subjective ESS. However, sleep-state misperception was no more frequent than in control subjects who had other hypersomnias or sleep apnoea.[75] These findings demonstrate that sleep misperception is a factum in PD patients as it is in individuals with chronic sleepiness due to other conditions.[73]

Management approaches

Recent years have seen several disappointments in neuroprotective therapy and it remains an important challenge to understand why very promising drugs have failed in human trials. Overall, sleep problems in PD remain a major therapeutic challenge.

Management of PD is complex, has to target underlying mechanisms, and comprises of non-pharmacological and pharmacological approaches. The first step is to identify at-risk patients.[76] To accomplish this, the physician or ancillary personnel must inquire about EDS from both the patient and carer, who might provide a more objective assessment of the patient's sleep habits as patients may not recognize that they are sleepy having become tolerant to the sensation of chronic tiredness. Therefore, management options for EDS and unintended sleep episodes include ensuring correct diagnosis by ruling out syncope, seizures, and cardiac disorder.

Non-pharmacological approaches can be the mainstay of treatment for mild to moderate EDS. As described, the use of a validated sleepiness scale, such as the ESS, provides a quick and reliable assessment of sleepiness based on the propensity of the patient to fall asleep in unintended situations, and does not rely on the patient's subjective awareness of whether or not they are sleepy. ESS scores greater than 10 are considered to be in the sleepy range, and such patients are at higher risk for experiencing unintended episodes of falling asleep.[76] Further management options include introducing proper sleep hygiene, eliminating unnecessary sedative medications, using the lowest dose of dopaminergic medication that provides satisfactory clinical control, identifying and treating sleep disorders, and counselling patients on risks of daytime sleepiness and sudden sleep episodes.[75] Patients with EDS should not drive a motor vehicle until this problem has been corrected. Indeed, European agencies have suggested that patients with PD taking dopamine agonists should not drive at all, although some experts believe that this recommendation is too harsh and that patients may safely drive, subject to specific treatment guidelines. PSG is the "gold standard" method used to evaluate sleep disorders and provides detailed information about actual sleep status. It can detect the co-occurrence of sleep apnea, restless leg syndrome-periodic leg movement in sleep (RLS-PLMS), and RBD. MSLT is helpful to quantify the severity of EDS. Good sleep hygiene is the cornerstone of effective management of any sleep disorder.

The management of Parkinsonian motor symptoms can be improved with the use of dopaminergic agents. If alterations in dopaminergic medications fail to help EDS, one can consider adding a wakefulness promoting agent like modafinil. Usually, mechanisms are multiple and treatment multimodal. Modafinil is a non-amphetamine drug well-established as a first-line, symptomatic treatment for EDS associated with narcolepsy and, more recently, is proving to be a useful agent in other medical conditions where EDS is a symptom. Whilst its mode of action is yet to be explained, modafinil appears to exert its effects specifically on the hypothalamus sleep-wake system, increasing wake promoting neuronal activity in the tuberomammillary nucleus (TMN) and decreasing sleep-promoting neuronal activity in the ventrolateral preoptic area (VLPO), thus inducing "calm wakefulness".[77] Early open-label reports were promising,[78,79] but double-blind controlled studies showed only modest[80,81] or no benefit.[82] In the clinic, the drug may be useful in treating EDS in individual

patients with PD. It should be started at a dose of 100mg and increased to 200–400mg per day as necessary. Side effects include insomnia, head pains, and depression. Depression should be evaluated and treated accordingly. Sometimes reassurance with or without supplementary psychotherapy is sufficient, but most often antidepressant medications are needed.

Further areas of research are now also focusing on adenosine A2A receptor antagonistsodium oxybate and caffeine to promote wakefulness. In the pursuit of improved treatments for PD, the adenosine A2A receptor was used as an attractive non-dopaminergic target.[83] This was based on compelling behavioral pharmacology and selective basal ganglia expression of this G-protein-coupled receptor. Its antagonists crossed the threshold of clinical development as adjunctive symptomatic treatment for relatively advanced PD. Adenosine derived from the degradation of adenosine triphosphate (ATP) or adenosine monophosphate (AMP) function as a signaling molecule in the nervous system through the occupation of A1, A2, and A3 adenosine.[84] Adenosine A2A receptors have a selective localization to the basal ganglia and specifically to the indirect output pathway, and as a consequence offer a unique opportunity to modulate the output from the striatum that is believed to be critical to the occurrence of motor components of PD. Several studies conducted worldwide report an inverse association between caffeine/coffee consumption and the risk of developing PD.[85] The association is strong and consistent in men, but uncertain in women possibly because of an interaction with hormone replacement therapy.[86] Palacios et al,[86] found that consumption of decaffeinated coffee was not associated with PD risk.

CONCLUSION

Improving patients' QoL is a key factor to consider when reviewing PD treatment plans since more than a half of PD patients report problems with sleep disturbances more than the motor symptoms of the disease, and EDS and unintended sleepiness has a large impact on the QoL of PD patients as well as their carers. There is no doubt that non-motor aspects of PD are of unquestionable relevance. As of today; however, options for their management are very limited. Prompt diagnosis should become standard in clinical practice, and management a research priority. Advice on good sleep hygiene is instrumental, as pharmacological approaches have yet to provide consistent and reliable results without significant adverse effects. The efficacy of pharmacological treatment of EDS in PD using wakefulness-promoting drugs, such as modafinil, remains controversial. Sleep attacks have been reported in patients taking dopamine agonists for conditions other than PD.[87]

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