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Sleep Disturbances in Parkinson's Disease

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Abstract

Sleep disturbances are very common in patients with PD and are associated with a variety of negative outcomes. The evaluation of sleep disturbances in these patients is complex, as sleep may be affected by a host of primary sleep disorders, other primary medical or psychiatric conditions, reactions to medications, aging or the neuropathophysiology of PD itself. In this article we review the evaluation of the common disturbances of sleep seen in PD. This includes the primary sleep disorders, the interaction of depression and insomnia, the impact that medications for PD have on sleep, as well as the role of factors such as nocturia, pain, dystonia, akinesia, difficulty turning in bed and vivid dreaming. The treatment of sleep disturbances in PD is largely unstudied but recommendations based on clinical experience in PD and research studies in other geriatric populations can be made. Important principles include, diagnosis, treating the specific sleep disorder or co-occurring disorder, and control of the motor aspects of PD.

Introduction

The physical aspects of Parkinson's disease (PD), such as tremor, rigidity and postural imbalance, have traditionally been regarded as the most important features of the disease and have understandably received the most attention in both research and clinical practice. Nonetheless, Parkinson's disease affects patients' lives in a broader sense than merely by physical impairment. For example, many of the non-motor aspects of PD, such as sleep disturbance and depression, are common and significantly affect the day-to-day lives of these individuals. Better treatment for these aspects of the illness could produce an important reduction in suffering.

Disturbances of sleep are highly prevalent in Parkinson's disease (PD), affecting up to 88 percent of community dwelling patients1 Furthermore, in studies that examine the impact of PD on quality of life (QoL), sleep difficulties are independent and important predictors of poor quality of life.2 In fact, most reports suggest that sleep disturbance, depression and lack of independence are the primary determinants of poor quality of life.3 In addition, sleep disturbances contribute to excessive daytime sleepiness (EDS) and poor daytime functioning as well as patients' reduced enthusiasm for daily events. Adverse effects have also been observed in the sleep habits and the quality of life of their spousal caregivers.4,5

Insomnia is defined as an almost nightly complaint of an insufficient amount of sleep or not feeling rested after sleeping. Obviously, the interactions between PD and sleep are complicated and many PD patients who complain of sleep disturbance may qualify for a diagnosis of

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insomnia though they have other primary sleep disturbances such as REM Sleep Behavior Disorder (RBD) or Periodic Limb Movements of Sleep (PLMS) and Restless Legs Syndrome (RLS). Furthermore, sleep disturbances may be related to factors such as depression, poor sleep hygiene, nocturia, pain, dystonia, akinesia, difficulty turning in bed, reactions to medications, and vivid dreaming.[6] If no other cause is found, the insomnia is classified as idiopathic. Daytime fatigue and excessive sleepiness may be related to insomnia, depression, medication effects, other medical illnesses as well as to other primary sleep disturbances such as Sleep Disordered Breathing (SDB). Thus an evaluation of a sleep problem in a patient with PD involves a systematic review of the differential diagnosis, and sometimes the use of a polysomnogram. In this article we review the common disturbances of sleep seen in patients with PD and also briefly discuss the treatment of these disorders.

Insomnia

Insomnia is generally divided into difficulty falling asleep (sleep initiation), staying asleep (sleep maintenance) and awakening too early in the morning. While all three problems occur in patients with PD, sleep maintenance difficulties are the most common, affecting up to 74–88% of patients.[1, 7]

While no specific trials have examined the treatment of idiopathic insomnia in patients with PD, both pharmacologic and non-pharmacologic measures have been shown to be beneficial in the treatment of insomnia in the general population and in the elderly. Pharmacotherapy is the most widely used treatment for insomnia in clinical practice.[8] In a survey of patients with PD living in the community, 40% were found to be using sleeping pills, compared to 23% of the non-PD controls.[9]

A variety of medications are available for use in patients with insomnia, including benzodiazepines, the non-benzodiazepine hypnotics, antihistamines and the sedating antidepressants. The benzodiazepines, such as temazepam, flurazepam and lorazepam are efficacious in short term use for sleep latency and for total sleep time.[10] While these medications are widely used and clearly effective, one should use them with caution in the elderly as they increase risk for fall and fractures by 50% or more.[11] In addition, benzodiazepines are associated with both tolerance and a risk of cognitive impairment in this age group.[12]

The nonbenzodiazepine hypnotics, such as zolpidem, eszopiclone and zaleplon, also work via the benzodiazepine receptor but have an improved side effect profile and are thus widely used today. They generally cause less confusion and morning sedation than the benzodiazepines, but caution is still advised in using these agents, as they have been associated with an increase in daytime sedation, abnormal sleep behaviors and falls.[13]

Sedating antidepressants, especially trazodone, are also widely used for insomnia,[14] though a recent review has questioned their efficacy.[15] Over the counter medications, such as the antihistamine diphenhydramine, are also commonly used and may be helpful for some patients.[16] A significant issue with both the sedating antidepressants and the antihistamines in PD is their anticholinergic effects, which may increase both constipation and cognitive impairment. Other over the counter aids, including herbal supplements, have not been studied and we generally do not recommend their use in individuals with PD.

In patients with significant cognitive impairment, psychosis or very vivid dreaming (often heralding daytime psychosis) the atypical antipsychotics quetiapine or clozapine may be of use. These medications have not been studied for insomnia in any patient group but they have been studied in PD for psychosis and are also used to treat a variety of disinhibited behaviors.[17] In general, PD patients tolerate these medications, but in very low doses. One must also be

cautious about sedation and a worsening of the motor components of the illness when using these medications in the PD population. An important consideration is that clozapine may only be used with frequent white blood cell monitoring (every week for the first six months) because of the risk of agranulocytosis.

Psychosocial treatments for insomnia are supported by controlled trials in patients without PD but appear to be rarely used in PD. There are advantages to these treatments, including that they are generally benign and free of adverse side effects and may engender more lasting changes following treatment cessation.[18] However, treatment can be costly and it may be difficult to find clinicians to administer it. Other new treatments that target the movements of PD may also have positive effects on sleep. For instance, deep brain stimulation (DBS), an effective therapeutic option for the treatment of advanced Parkinson's disease, has been shown to improve sleep in PD.[19]

REM behavior disorder (RBD)

RBD is a syndrome of abnormal behavior during rapid eye movement (REM) sleep. Under normal circumstances, voluntary muscles are atonic when one enters REM sleep. However, the absence of this normal atonia in patients with RBD leads to the acting out of dreams. Thus, an individual who experiences being chased in a dream may flee the bed or attempt to punch his pursuer. The response may range from relatively mild restlessness to more severe wild punching and thrashing in which patients may leap out of bed or strike their bed partner. Thus, RBD is potentially dangerous for the patient and his or her bed partner and prompt identification and treatment is warranted.

RBD, of varying degrees of severity, occurs in 15–50% of patients with PD; the higher rates are found when patients are studied with polysomnograms (PSG).20 RBD is likely the result of degenerative changes in the brain and many patients with RBD go on to develop PD or dementia.21 It is, therefore, thought that RBD often reflects an underlying common pathology (synucleinopathies) across neurological illness.22

There are few data on treating RBD in patients with PD. In one widely cited study using clonazepam, a long acting benzodiazepine, Schenck et al.[23] reported that 90% of the 57 treated patients improved on moderate doses. Another small case series describes melatonin as useful.[24] Because of the study by Schenck, et al., and clinical experience, clonazepam is currently the standard treatment for RBD in patients with PD. One does, however, need to remember the caution concerning benzodiazepines, sedation and confusion.

Sleep Disordered Breathing

Sleep disordered breathing (apnea) may occur from a deficit in breathing drive in the brain (central sleep apnea) or a problem with the passage of air through the breathing passages (obstructive sleep apnea - OSA). As breathing becomes more difficult or ceases a decrease in blood oxygen level results, which in turn results in sufficient awakening to restore breathing. As the patient remains in light sleep, they may be unaware of these awakenings which may occur hundreds of times a night. Consequently, the patient experiences little deep restorative sleep at night and extreme daytime sleepiness. Because the patient may be unaware of the problem, one needs to query a bed partner who will be aware of loud snoring, gasping and periods of no breathing.

Apnea has been found in as many as 50% of patients with PD.25 Snoring and apneic episodes also may be up to three times more common in PD (12%) than in the general population.[7] The treatment of sleep apnea involves, first, the identification of the problem through clinical vigilance, and then confirmation with a polysomnogram. Although some may be resistant to

the idea of staying overnight in a sleep center hooked to a variety of sensors, patients should be reassured that most people find the polysomnogram experience to be non-aversive. Patients with apnea then have a variety of treatment options, generally administered through a sleep center. These may involve nighttime appliances, like CPAP (continuous positive airway pressure) machines, among others.

Restless Legs Syndrome (RLS) and Periodic Leg Movements of Sleep (PLMS)

Persistent motor symptoms that occur during sleep include periodic limb movement of sleep (PLMS) and restless legs syndrome (RLS). RLS tends to occur at the beginning of sleep or as one is trying to fall asleep and presents as a disagreeable restless feeling that is often only relieved by moving ones legs. PLMS are rhythmic moving or jerking of the limbs during sleep. Both of these disorders may interfere with the quantity and quality of sleep. RLS and PLMS are common in patients with PD, occurring in up to 15% of patients, and can lead to disrupted sleep and excessive daytime sleepiness.[26]

If tolerated, an increase in dopaminergic treatment at night is helpful with RLS and PMLS, as they decrease periodic limb movements during sleep and significantly improve early-morning motor function.[27] Ropinirole and pramipexole have recently been approved for use in the US for RLS. Other treatments that have received some support include benzodiazepines and the opiates.[28]

Vivid Dreaming

An increase in dreaming is common in PD, with studies suggesting that about 30% of patients develop vivid dreams on dopaminergic therapies.[29] Because vivid dreams are often a prodrome of daytime hallucinations[30], one should query patients about this phenomenon. Many patients do not find vivid dreaming to be a significant problem and may not want to expend effort in treatment. As the problem is generally related to dopaminergic therapy, the first approach may be to reduce the nighttime dopaminergic dose. If this is neither tolerated nor helpful, the addition of the atypical antipsychotic quetiapine can be considered.

Excessive Daytime Sleepiness (EDS) and Fatigue

Tiredness during the day is one of the more common difficulties experienced by people with PD. EDS (the tendency to fall asleep during the day) should be differentiated from fatigue (difficulty in initiating and sustaining mental and physical tasks). While it can be difficult to clinically distinguish fatigue and tiredness, the distinction is possible with Multiple Sleep Latency Test (MSLT) done in a sleep lab. Estimates of the occurrence of EDS range from 15–50%[31] and fatigue is found in up to 59% of patients.32 The presence of both EDS and fatigue are significantly correlated with more severe disease, more disability, cognitive decline and depression.33

There are a variety of possible explanations for the high rates of both EDS and fatigue in PD. Included in these possibilities are insomnia, the effects of aging, sedating effects of medications, an effect of the central illness on sleep and wake centers in the brain, intrinsic sleep disorders such as apnea, and the presence of comorbid illness such as depression. The main causes of EDS and fatigue that should be considered in treatment planning are insufficient or unsatisfactory sleep, comorbid medical and psychiatric disorders and the effects of drug therapy. Therefore, the first approach is to evaluate the patient's sleep. A review of medical and psychiatric disorders, such as depression and anxiety should also be a priority. Because many other non-PD medications that patients take may also induce EDS and fatigue, it is necessary to review the entire medication list. Special attention should be directed to the direct dopamine agonists as discussed below.

Treatment may also include a variety of environmental and behavioral approaches that, while not studied in PD, have been found to be helpful in other populations. Regular mild exercise is a mainstay of the treatment of fatigue and should usually be recommended. A stimulating daytime environment and exposure to intense light in early morning may be of use. Stimulant medications should be considered in refractory situations. Small controlled trials of modafinil have found a modest effect on EDS in PD patients.[34] Other stimulants, such as methylphenidate, may improve EDS and fatigue, though there are no controlled studies addressing this issue.

Sleep Attacks

Sleep attacks are abrupt and unavoidable transitions from wakefulness to sleep. These "attacks" are of particular concern as the patient may have little warning that they are about to fall asleep. Obviously, if these attacks occur during potentially dangerous activities, such as driving or walking down stairs, harm may result.

The prevalence of sleep attacks in patients with PD varies across studies, from 0 to 30%.[35] While the issue has been debated, sleep attacks are probably a class effect of all dopamine agonists and probably all dopamine replacement therapies. Given the potential for harm, an inquiry into the presence of sleep attacks should be a routine in all patients with PD.

Treatment of sleep attacks involves a number of approaches. The first is to identify the problem by systematic patient inquiry and then to educate patients about the risks associated with the sleep attacks and to identify behavior changes that may need to be made (i.e., eliminating driving). One should also consider reducing or eliminating the direct dopamine agonists if sleep attacks are occurring with little warning or are significantly affecting functioning. As sleep attacks generally occur in the context of EDS, one should also address this problem.

Relationship between Depression and Sleep in Parkinson's Disease

Depression is one of the two most common causes of insomnia[36] and depression is very common in PD.[37] The relationship between depression, sleep and fatigue is complex and not well understood. Insomnia may be a direct result of depression or may be secondary to the drugs used to treat the depression. Depression can cause fatigue though fatigue can result from directly form insomnia and fatigue or excessive daytime sleepiness can result from the drugs used to treat the depression.

While the effects of depression on sleep in PD patients have not been carefully studied, surveys have confirmed what is clinically apparent; patients with PD and depression have more difficulty with sleep.[38] It is, therefore, prudent to assume that depression will adversely affect sleep and that treatment for depression must be optimized.

The Etiology of Sleep Disorders in Parkinson's Disease

The interactions between PD and sleep are complicated. First, many of the degenerative changes that are occurring in the brain may directly affect sleep/wake mechanisms and lead to sleep disruption.39 In particular, brain neurotransmitters that mediate sleep functions (norepinephrine, serotonin, dopamine and GABA) are variably damaged in PD.[40] Furthermore, neurotransmitters involved in REM sleep (acetylcholine, serotonin and norepinephrine) are also variably disrupted in PD. Motor difficulties, such as inability to move in bed, dystonic movements, and pain from leg cramps may all interfere with sleep maintenance. While dopaminergic replacement therapy may improve sleep in patients experiencing nighttime motor dysfunction, it can also disrupt normal sleep architecture and may be stimulating to some patients. As previously discussed many other primary sleep disorders, such as sleep apnea,

restless legs, etc., occur commonly in individuals with PD. Superimposed on these complex interactions are age related sleep and circadian changes. Approximately 40% of the elderly experience sleep difficulties and these problems tend to be more common in those elderly with physical and psychological problems.41

Conclusions

Sleep problems are very prevalent in PD, affecting about three quarters of these individuals. The disturbance most often involves difficulty staying asleep through the night, but may affect virtually any aspect of sleep. Other co-occurring sleep disorders, such as sleep apnea, REM behavior disorder and restless legs syndrome are also very common. These sleep problems are associated with poor quality of life for both the patient and the caregiver.

The treatment of sleep disturbances in PD is largely unstudied but recommendations based on clinical experience in PD and research studies in other geriatric populations can be made. The first step is proper diagnosis. The next step is to treat the specific sleep disorder or the co-occurring disorder that is interfering with sleep, as many conditions, such as RBD, RLS, etc. have specific treatments. Special attention should be paid to depression, which frequently travels with PD and nearly always interferes with sleep. The control of the motor aspects of PD must also be paramount, as nighttime movements will interfere with sleep.

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