

Sleep disorders in Parkinson disease

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Introduction

Parkinson disease is a progressive degenerative disease causing motor and non-motor symptoms. Sleep disturbance is a common non-motor symptom and significantly affect the day to day activities of patients and their quality of life. Though common, sleep disturbance is an under diagnosed feature of Parkinson disease (PD). Night-time sleep disturbances have been reported in as many as 60 to 98% of patients with Parkinson disease^{1,2}. Patients with Parkinson disease have more complaints of sleep disturbances and poor quality of sleep than age matched controls^{2,3,4}. In addition to night time sleep disturbances about 50% of Parkinson patients also complain of increased excessive day time sleepiness compared to age matched controls^{5,6,7}. Sleep disturbances in Parkinson disease may be due to the disease or secondary to medication. Associated conditions like depression and age related disorders also play a role in sleep disturbances in these patients.

Parkinson disease associated sleep disorders are unrecognized by physicians whose attention is mainly focused on the motor symptoms. Detailed assessment of sleep and sleep disturbances are often omitted in a busy consultation. The patient and the care givers do not report sleep disturbances to the physician as they fail to recognize them as a part of the disease. As a result the patient unnecessarily endures treatable sleep disorders for long periods of time. An increased awareness and aggressive treatment of sleep disorders in patients with Parkinson disease will result in a better quality of life for both the patient and the caregivers.

Nocturnal sleep disturbances in Parkinson's disease could be due to many reasons such as nocturnal recurrence of Parkinson symptoms such as tremor, difficulty in turning over in bed, rigidity and painful cramps. Other common causes for sleep disturbances are due to conditions associated with

Parkinson disease such as depression, anxiety, restless leg syndrome, periodic limb movement disorder, rapid eye movement (REM) behavior disorder, dementia, sleep apnoea and excessive day time napping. Anti-Parkinson medication especially dopamine agonists induce insomnia. It is also a side effect of medications such as selegiline, anticholinergics and amantadine. Vivid dreams, nightmares and hallucinations are side effects of anti Parkinson medication and these disturb sleep.

In addition to Parkinson disease these patients also have other co-morbidities. Sleep disturbances occur as a result of these co-morbidities or due to the medications. Withdrawal from sedatives or hypnotics, emotional conditions like stress, anxiety and reaction to major life events also can result in sleep disturbances in patients with Parkinson disease.

Sleep fragmentation

Sleep fragmentation is characterized by frequent awakening and is common in Parkinson disease. A survey carried out in UK showed that 76% of 220 patients with PD had nocturnal sleep disturbances due to many causes including frequent micturition, inability to turn over in bed, painful leg cramps, tremor and foot dystonia⁸. In patients with advanced disease, the effect of the day time medication wanes off towards the evening resulting in increased muscle rigidity, slowness, stiffness and tremor. A careful history will reveal the nocturnal symptoms of Parkinson disease.

Sleep fragmentation may improve with nocturnal use of levodopa^{9,10,11}. Sustained release levodopa preparations have proven to be beneficial¹¹. Nocturnal use of levodopa also helps to alleviate the morning symptoms and disability of PD¹⁰. More recent studies also support the evidence of sleep improvement with levodopa/carbidopa intestinal gel infusion¹². Catechol-O-methyl transferase (COMT) inhibiting compounds such as entacapone will prolong the levodopa levels and help reduce night time symptoms. COMT inhibiting compounds will only be effective in patients already on levodopa and will not have any effect if the patient is on any other medication. Recent studies have shown that once daily prolonged release ropinirole (2-24 mg/day) improve symptoms in patients with

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advanced PD who suffer troublesome nocturnal disturbances not optimally controlled with levodopa¹³. Studies have shown that nocturnal activity is greater in PD patients treated with levodopa or dopamine agonists^{14,15}. However some other studies report that while nocturnal sleep improves with levodopa daytime sleepiness may increase¹⁶.

Sleep fragmentation due to sleep apnoea

About 20 to 40% of patients with PD have been observed to have sleep apnoea^{17,18}. Obstructive sleep apnoea was the commonest type. However the PD patients with obstructive sleep apnoea had a normal body mass index compared to non Parkinson patients with obstructive sleep apnoea^{17,19}. PD patients with sleep apnoea may present with only excessive day time sleepiness. Care givers may report excessive snoring or gasping and choking. Presence of snoring is a predictor of daytime sleepiness²⁰. Obstructive sleep apnoea is managed with continuous positive airway pressure (CPAP). Patients who are excessively sleepy without a clear cause or those with a history suggestive of obstructive sleep apnoea should be evaluated by polysomnography. Some studies have shown that patients with multi system atrophy have nocturnal apnoea with glottis closure resulting in stridor²¹ and these patients respond poorly to CPAP. These patients may need tracheostomy and is usually a life saving procedure.

Sleep fragmentation due to Restless Legs Syndrome and Periodic Limb Movements during sleep.

Restless leg syndrome (RLS) is a clinical diagnosis, where the patient gives a subjective report of an urge to move the legs, accompanied by an uncomfortable or unpleasant sensation in the legs. The urge to move occurs with rest and is relieved with movement. This occurs or worsens in the night or towards the evening²². RLS is common in Parkinson disease^{7,20,23}. However the occurrence of RLS may be similar in frequency to an age matched population without PD²⁰ and may have an association with lower ferritin levels which is seen in non PD patients. PD patients have been reported to have low ferritin levels²³. Moderate to severe RLS responds to direct dopamine receptor agonists²⁴. Levodopa is an effective treatment for RLS but often leads to worsening of RLS symptoms with augmentation²⁵. If serum ferritin is low iron replacement can be considered as it has been effective in reducing RLS in non PD patients²⁶.

Periodic limb movements during sleep (PLMS) occur primarily during non-rapid-eye-movement (non-REM) sleep. It is characterized by an intermittent

rhythmic movement of the legs (triple flexion of hip, knee and ankle). This can result in arousal and awakening if severe. PLMS may be more frequent in PD and increases with more severe PD²⁷.

Direct acting dopamine receptor agonists appear to be superior to levodopa in the management of PLMS and RLS. With dopamine agonists there is reduced occurrence of rebound (RLS symptoms occurring at the end of the effect of a single dose of levodopa) and augmentation (RLS symptoms occurring at an earlier time in the evening, often associated with spread to other body areas and more severe symptoms). Opiates and benzodiazepines have also shown to be effective²⁸.

Other causes for fragmented and delayed sleep

Depression is common among PD patients. Depression causes sleep disturbances in the early REM period in non PD patients. Managing depression with tricyclic antidepressants like amitriptyline and nortriptyline in small doses in the evenings is beneficial with their sedating side effects^{29,30}. However tricyclic antidepressants may cause worsening of RLS and PLMS and may initiate or worsen night time hallucinations. Zolpidem at bed time for a short period helps PD patients with situational anxiety or acute insomnia with no other recognizable cause. There is no rebound insomnia after discontinuation³¹.

Hallucinations syndrome in PD patients on chronic dopaminergic therapy

About 25% to 40% of PD patients on long term dopaminergic therapy develop drug induced visual hallucinations³². Dementia, sleep disturbance, depression, visual disturbances and axial predominance of motor signs are associated with hallucinations^{33,34,35}. Fragmented sleep is not specifically associated with hallucinations, however vivid dreams may be.

The visual hallucination may be alleviated by discontinuing drugs with central effects that are not essential to patient care such as anticholinergic agents, anxiolytics and centrally active pain medications such codeine and antidepressants. Provision of a night light might be useful. Reduction in the dopaminergic drug dose and the avoidance of the evening dose may be considered but this may lead to the worsening of motor symptoms. Changing from direct dopaminergic agonist to shorter acting levodopa may be tried. If dopaminergic medication cannot be reduced atypical antipsychotics may be tried. Clozapine has been shown to be effective and other atypical antipsychotics like quetiapine have been used but appropriate monitoring for side effects are needed.

REM Sleep Behaviour Disorder

REM sleep behavior disorders (RBD) are associated with PD and other Parkinsonian syndromes. It may predate the onset of Parkinson disease, develop with or after the onset of PD. RBDs were first described in 1986 by Schenck and colleagues³⁶ is characterized by the presence of the following minimal diagnostic criteria in the revised International Classification of Sleep Disorders (ICSD). There should be electromyographic evidence of maintained muscle tone in submental muscles or excessive activity in limb muscles during REM sleep with one of the following; sleep related injury or disruptive behavior by history or abnormal sleep behavior during polysomnography³⁷. Caregivers may report that dreams appear to be acted out. The dreams recalled during episodes of REM sleep behavior disorder are aggressive and violent and may lead to injury^{38,39}.

REM sleep behavior disorder may occur sporadically with a flurry of episodes occurring on a daily basis followed by a period of quiescence. Longitudinal assessment of PD show that RBD symptoms can vary over time and also has a tendency to increase during early stages of the disease. Presence of RBD symptoms could be a risk factor for motor function deterioration particularly of bradykinesia⁴⁰. Patients dream of being chased, threatened or trapped and this leads to behaviours such as punching, choking, kicking or jumping out of bed and patients have sustained injuries^{39,41}. Bed partners are also at risk of injury and are frightened by the sudden and violent behavior. These symptoms are revealed only on questioning by the physician as the patient does not remember the episode and the caregiver does not recognize them as a part of the disease.

REM sleep behavior disorders occur in 15 to 32% of PD patients³⁹. PD patients evaluated with polysomnography showed that 33% had REM sleep behavior disorder and 58% had evidence of loss of muscle atonia during REM sleep⁴². Thus about 50% of patients with PD may have subclinically or clinically manifest REM sleep behavior disorder⁴³. Studies have also shown that 33% of PD patients may manifest REM sleep behavior disorder symptoms prior to the onset of motor manifestations⁴⁴. SPECT studies showed that patients with primary REM sleep behavior disorder without PD have abnormalities with olfaction and nigrostriatal degeneration. This supports the theory that REM sleep behavior disorder may predate motor manifestations of PD. REM sleep behavior disorder is more frequent in multi system atrophy and dementia

with Lewy bodies^{45,46,47} where there is more extensive brainstem and cortical pathology.

Treatment of REM sleep behavior disorder is indicated when symptoms disrupt sleep of the patient or bed partner or cause injury. There are not many controlled trials and the evidence is from case series. Clonazepam commencing at low doses of 0.25 mg may reduce the symptoms but may cause confusion in the elderly patients. There is some evidence that donepezil, pramipexole, quetiapine and melatonin may be beneficial^{48,49,50}.

Excessive day time sleepiness in PD

Excessive day time sleepiness is common in PD with a community based study showing excessive day time sleepiness in 15.5% of patients with PD 51. Many factors are associated with excessive day time sleepiness including anxiety, advanced PD and longer disease duration, male gender and orthostatic hypotension. Excessive day time sleepiness is also associated with the use of dopamine agonists. All dopaminergic drugs lead to day time sleepiness and sleep attacks. In addition to sleep disorders a sedentary life promotes excessive day time sleepiness and reversal of sleep pattern. Anti parkinsonian medication specially levodopa and dopamine receptor agonist^{16,39,52} increase day time sleepiness. These patients may also be on other medications for medical comorbidities and these may also increase day time sleepiness.

Restoring normal sleep pattern would be the aim in managing excessive day time sleepiness. Strategies to establish good sleep hygiene include established bed time and wake up times with exposure to adequate light by the day and darkness at night. Exposure to sunlight to promote circadian rhythm is useful. Physical exercise should be encouraged, but strenuous exercise should be avoided 3-4 hours before sleep. A hot water bath and relaxation techniques promote sleep at night and thus reduce day time sleepiness.

Sleepiness due to anti Parkinsonian medication may be difficult to control. Dose reduction may be tried but motor symptoms may worsen. Sudden onset irresistible urge to sleep (sleep attacks) is associated with dopamine agonists pramipexole, ropinirole and pergolide^{53,54,55} and switching to another agonist or discontinuing the medication may be effective. Patients with day time sleepiness not responding to above measures may benefit from amphetamine metabolites of selegiline, small doses of methylphenidate modafanil.

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