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Pyramid Journal of Medicine
Pyramid Journal of Medicine 2026; 9:549
doi:10.4081/pjm.2026.549

Daytime sleep disorders among patients with Parkinson's disease in a tertiary medical centre in Kano, Northwestern Nigeria

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Abstract

Parkinson's Disease (PD) is commonly associated with sleep disorders, which may manifest years before disease diagnosis. Excessive Daytime Sleepiness (EDS) is a common problem seen in People with PD (PwPD) which is found to worsen by the presence of concomitant insomnia (sleep fragmentation, shortened sleep duration, early awakening) and anti-Parkinson's medications. Identifying its presence and provision of appropriate intervention could significantly improve their Quality of Life (QoL). Using a cross-sectional study design, 100 PwPD and 100 healthy controls were enrolled over a period of 10 months to assess the prevalence of EDS using the Scales for Outcome in Parkinson's Disease-Sleep (SCOPA-S) diagnostic tool. The SCOPA-S index questionnaire identified EDS in 64% of PwPD who have significant daytime sleepiness, including falling asleep unexpectedly either during the day or in the evening (U=1722.5, p<0.05), while sitting peacefully (U=279, p<0.05) or while talking to someone (U=2652, p<0.05) or had trouble staying awake during the day or in the evening (U=2769, p<0.05) in the past 1 month when compared to their controls. However, falling asleep while reading or watching television (U=3451.5, p=0.08) and whether patient perceives falling asleep during the day in the last one month as a problem (U=3473, p=0.064) did not differ between the 2 groups. The high prevalence of excessive daytime sleepiness among PwPD from the study should prompt all physicians on early detection aimed at improving their overall care and quality of life.

Key words: Parkinson's disease, excessive daytime sleepiness, sleep disorders.

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Introduction

Parkinson's Disease (PD) is a chronic neurodegenerative disease, attributed mainly to the loss of dopaminergic neurons in the substantia nigra pars compacta with the first symptoms occurring after loss of 60% of these neurons and known for its four cardinal features of bradykinesia, resting tremor, muscular rigidity and postural instability.[1] Initially thought to be a motor disorder, it is now known to be associated with non-motor symptoms. Sleep disorders which are underdiagnosed are some of the earliest non-motor symptoms, occurring as early as 10 years before the actual diagnosis of PD is made.[2,3] They can be categorized broadly into diurnal sleep disorders and nocturnal sleep disorders with the former commonly including Excessive Daytime Sleepiness (EDS) and sleep attacks.[4]

EDS is an involuntary, irrepressible, undesirable and inappropriate sleepiness or drowsiness that occurs while awake, such that People with PD (PwPD) feel sleepy or drowsy most of the day, the etiology of which is not completely understood.[5,6] There is growing evidence of data showing that EDS is a common problem in PwPD, reported to have a prevalence of 50% in a study of 168 PwPD, EDS was reported in 25% compared to 8% in controls[7] in a similar study. In a review of published literature written over ten years, the prevalence of EDS was 15-50% and this variation was due to the definition across the studies.[8] The cause in PwPD is presumed to be multifactorial from intrinsic abnormalities of the disease and the soporific effect of dopamine agonist medications used to treat the disease. The chronic use of levodopa and dopamine agonists and their effect on the ventral tegmental nucleus is believed to increase melatonin concentrations and lowering the threshold for sleep in the daytime.[9] Both have a biphasic effect on sleep and wakefulness depending on their concentrations. Low doses of these medications enhance sleep via its effect on dopamine D2 inhibitory auto-receptors while higher doses reduce the third stage of sleep (slow wave sleep) thereby promoting alertness by activating dopamine D2 receptor agonist suggesting an imbalance in the activated D2 receptors either from a loss of D1 dopamine receptors or increased D2 dopamine receptors as well as a reduction in serotonin transporter availability in the raphe nuclei, the thalamus, putamen, caudate nucleus and the ventral striatum in PwPD could cause EDS.[8,10] A disorder of the sleep wake system resulting from the neurodegenerative process is characteristic of PD and has been observed to involve 37-55% of the serotonergic raphe nuclei, 32-46% of the basal forebrain cholinergic system of the nucleus basalis of Meynert, 46% of the pedunculopontine tegmental nucleus and 63-78% in the noradrenergic locus coeruleus as well as degeneration of dopamine neurons of the pars compacta that project to the thalamo-cortical circuitry to promotes arousal and feedback to the reticular activating system along with the ventral tegmental area and the ventral periaqueductal gray mat-

ter, have been implicated in the pathogenesis of EDS. Genetic predisposition has been reported for EDS in PwPD who are positive for HLA allele for narcolepsy DQB1*06:02 as they are also more likely to develop EDS than PwPD without the allele.[10] Excessive daytime sleepiness is a common non-motor symptom seen in males with non-tremor dominant PD and usually on dopamine agonist.[5] It could be the result of insomnia, Rapid Eye Movement (REM) sleep Behavior Disorder (RBD), Restless Legs Syndrome (RLS) or any disorder of sleep regulatory centers in the hypothalamus and brain stem. Studies on the negative impact affecting the Quality of Life (QoL) of PwPD with EDS have focused mainly on the physical, vegetative and psycho-social functioning.[10] It can impair attention, balance, and reaction time, which when combined with bradykinesia and postural instability increases the risk of disastrous falls leading to fractures, long-term hospitalization, and attendant complications of immobility. Additionally, it is linked to hormonal imbalances (insulin resistance and dysregulation of hunger hormones (ghrelin and leptin) which can lead to weight gain, increased diabetes risk, and poor nutritional habits. Furthermore, chronic EDS have been shown to promote earlier development of mild cognitive impairment, exacerbate neuropsychiatric symptoms (depression, anxiety and social withdrawal) and increased caregiver burden. Diagnostic screening tools used in the assessment sleep disorders have been developed to aid identification by general physicians.[11] They are less expensive and easier to administer especially in our resource-challenged setting, when compared to the cost-intensive neuroimaging techniques and sleep polysomnography, which remains the best assessment tool for sleep disorders. The Scales for Outcomes in PD-Sleep (SCOPA-Sleep) is a validated PD-specific instrument that provides a comprehensive assessment of both Nocturnal Sleep Disturbances (NS) and Daytime Sleepiness (DS), including sleep fragmentation, which is a primary complaint that is not captured by most other sleep scales focusing solely on daytime sleep propensity.[12] As sleep disturbances in PD is not just about sleepiness; but the combination of motor symptoms (tremor, stiffness), non-motor symptoms (anxiety, depression, dementia, nocturia, pain), and anti-PD medication side effects that can disrupt sleep, which makes it more complex to assess using simple generic daytime assessment tools. However, SCOPA-S has the primary advantage of capturing these complexities, for both short- and long-term PD making it more suitable in interventional studies due its strong psychometric and discriminant properties between subjects and controls and patients in different stages of PD stages.[11] It is scale that includes 12 items to measure sleep quality, NS, and DS. The NS subscale includes 6 items on insomnia, multiple awakenings, sleep efficiency, and duration plus one single item on overall sleep quality, where a cut-off score of 7 has shown excellent sensitivity and specificity. The internal consistency of the NS subscale is high (Cronbach's alpha =0.88-0.84), and test-retest reliability is excellent (ICC=0.94). The DS subscale includes 6 items on unexpected sleep attacks, dozing off in daily situations and difficulty staying awake. Items are scored from 0 to 3, with total scores ranging from 0 to 18 points where higher scores indicate more severe problems. The internal consistency of the DS subscale is also good (Cronbach's alpha =0.91-0.75) with a robust test-retest scores (ICC=0.89). The paucity of data on understanding sleep disorders in PwPD from Northern Nigeria prompted the need for this study, which is aimed at improving their overall care and quality of life.

Materials and Methods

We conducted a cross-sectional study where 200 participants (100 PwPD and 100 age and sex matched healthy controls, mainly volunteers or unrelated spouses without PD of patients) were consecutively enrolled from the neurology and family medicine clinics of Aminu Kano Teaching Hospital respectively, over a 10-month period. Informed consent was obtained from participants or from their legal proxies. Appropriate approval was obtained from the hospital research and ethics committee before commencement of the study (NHREC/28/01/2020/AKTH/EC/2841).

Diagnosis of Parkinson's disease was made using the UKPDS Brain Bank clinical diagnostic criteria.[13] This includes, (i) at least two of three cardinal signs of tremor, rigidity, bradykinesia (with or without postural or gait abnormality), (ii) an asymmetric onset, (iii) responsiveness to levodopa therapy. Participants with neurodegenerative disease, such as multiple system atrophy, progressive supranuclear palsy, corticobasal syndrome, vascular parkinsonism, and Lewy body dementia, *etc*., were excluded from the study. Additionally, participants with clinical features of any condition that could affect sleep, such as obesity, obstructive sleep apnea, anxiety, depression, and gastro-esophageal reflux disease, were also excluded. The SCOPA-S questionnaire was used to assess the presence of sleep disorders in PwPD.[12]

The data obtained was analyzed with the Statistical Package for Social Sciences (SPSS) (IBM Inc., Armonk, USA) version 23. Quantitative variables were described using mean and standard deviation and qualitative variables were presented as percentages. Where appropriate, non-parametric test X^2 (or Fisher exact test) was used to compare proportions. For parametric continuous data: Mean was used to summarily describe the data, mean of two groups was compared using student t-test. For non-parametric continuous or ordinal data such as sleep scales, the data was described using median and comparison between median values of two groups was done using Mann Whitney U test.

Results

Two hundred participants (100 PwPD and 100 age and sex matched controls) were enrolled in the study. Their ages ranged between 41 to 90 years with a mean age of 66.8 years. The PwPD have higher proportion of individuals with nonformal education (65/116), while the healthy controls have a higher proportion with tertiary education (34/50). Additionally, the PwPD arm have a significantly higher proportion of individuals who consume alcohol (22/31) when compared to their control (Table 1).

The questionnaire identified 64% of PwPD with excessive daytime sleepiness while 23% of controls reported excessive daytime sleepiness. All the SCOPA-S nighttime items were found to be statistically significant when compared to their controls ($p<0.05$) as shown in Table 2. Early awakening was the most prevalent sleep disorder in the cases group (84%), and it was entirely absent in the controls group. This finding is statistically the most significant ($X^2=141.4$, $p<0.0001$*).

PwPD experience significantly more daytime sleepiness, including falling asleep unexpectedly or during sedentary activities (p-value<0.05). However, SCOPA-S daytime items for assessment of falling asleep while watching television or reading and if patient perceive falling asleep during the day sleepiness in the last one month to be a problem, did not show any statistical difference among the two groups (p-value>0.05) as shown in Table 3.

Discussion

The high prevalence of EDS in this study confirms that it is a common problem seen in PwPD. This was higher than 30.6% found in Port Harcourt, South-South Nigeria,[14] 47.1% in Ethiopia,[15] 49% found in Pakistan,[16] 37.8% found in Japan,[8] 33% found in Austria,[17] 25% found in France,[7] and 15.5% reported in Norway.[9] Use of various tools for sleep disorder assessment seen in most of these previous studies could account for the variable figures observed above, although all were within the prevalence ranges seen in PD globally. Furthermore, variations may be explained by the higher PD prevalence figures observed speculatively due to differences in environmental risk exposure, genetics, or sociocultural factors.[18,19] The study showed high frequency of other sleep disorders especially insomnia, which also corroborates the frequent co-existence of more than one sleep disturbances in PwPD as documented from previous studies from Nigeria.[20]

The SCOPA-S scale was able to discriminate between PwPD and controls, and the results was similar and comparable with the results seen with other standardized sleep questionnaires.[21] Most of the PwPD in the study were on monotherapy with levodopa and therefore assessing the role played by the medication as opposed to the extent of disease severity in the pathogenesis of EDS was not done. However, it is worthy to note that previous studies have not shown any difference in terms of increased daytime sleepiness between PwPD on monotherapy or polytherapy.[7] It is also paramount to state that with the use of composite tools as done in the index study, it is difficult to definitely postulate that EDS observed is a side effect of medications or simply a clinical manifestation of neurodegeneration consistent with PD. Our study is the first to assess sleep disorders in Northern Nigeria, which provides the basis for establishing a protocol on early screening as part of routine clinical evaluation by both family physicians and specialists,

Table 1. Socio-demographic characteristics of the study population.

Variables	Cases (n=100)	Control (n=100)	Total (n=200)	X^2	p
Gender					
Female	30	30	60	0.00	1.000
Male	70	70	140		
Occupation					
Trader	21	20	41	0.17	0.999
Farmer	40	40	80		
Engineer	5	5	10		
Judicial staff	3	3	6		
Police	4	4	8		
Housewife	5	5	10		
Teacher	3	4	7		
Secretarial staff	19	19	38		
Educational status					
Informal	65	51	116	12.41	0.006*
Primary	15	7	22		
Secondary	4	8	12		
Tertiary	16	34	50		
Ethnicity					
Hausa	89	89	178	0.00	1.000
Ibo	6	6	12		
Yoruba	2	2	4		
Others	3	3	6		
Marital status					
Married	97	97	194	0.00	1.000
Divorced	1	1	2		
Widowed	2	2	4		
Income (N)					
<50,000	68	67	135	0.02	0.988
50,000-150,000	29	30	59		
>150,000	3	3	6		
Diabetes					
Yes	8	10	18	0.24	0.621
No	92	90	182		
Hypertension					
Yes	11	15	26	0.71	0.400
No	89	85	174		
Alcohol intake					
Yes	22	9	31	6.45	0.011*
No	78	91	169		
Cigarette smoking					
Yes	4	7	11	0.38	0.535
No	96	93	189		

*Statistically significant at p-value of <0.05, X2= Chi-square.

aimed at providing optimal treatment options to improve overall care especially in our resource constraint setting.[22] The findings should be interpreted within the limitations of it being a hospital-based study and cross-sectional in design where relationship between cause and effect cannot be inferred. Therefore, longitudinal studies are needed to further evaluate the consequences of central determinants (non-motor symptoms including psychiatric and neurologic symptoms as well as sedative effects of dopamine agonists) of EDS in our setting, as shown by some previous studies.[23,24] Further studies with less expensive actigraphy using ring or wrist based devices that monitor sleep wake patterns and quality or the sleep video-polysomnography in combination with Electroencephalogram (EEG), Electro-Oculography (EOG), airflow via nasal pressure and naso-oral thermistor, respiratory efforts (via thoracic and abdominal plethysmography), transcutaneous oxyhemoglobin, body position, tracheal sound (snoring detector), as well as synchronized infrared video and ambient sounds are needed to better characterize EDS, which are currently unavailable in our resource challenged setting.

Conclusions

The high prevalence of EDS among PwPD calls for the need by all stakeholders involved in their management to adopt methods that would have a positive impact on their overall care aimed at reducing the emotional, physical and psychological burden on their family and other care givers.

Table 2. Prevalence of sleep disorders using Scales for Outcome in Parkinson's Disease-Sleep (SCOPA-S).

Variables	Cases (n=100)	Control (n=100)	Total (n=200)	X^2	p
Excessive daytime sleepiness					
Present	64	23	87	44.3	<0.0001
Absent	36	77	113		
Insomnia					
Present	76	29	105	34.2	<0.0001
Absent	24	71	95		
Sleep fragmentation					
Present	67	15	82	55.9	<0.0001
Absent	33	85	118		
Shortened sleep duration					
Present	77	09	86	94.3	<0.0001
Absent	23	91	114		
Early awakening					
Present	84	00	84	141.4	<0.0001*
Absent	16	100	116		
Poor quality of nighttime sleep					
Present	80	17	97	79.5	<0.0001
Absent	20	83	103		

*Statistically significant at p-value of <0.05, X^2= Chi-square, α using Yates corrected Chi-square.

Table 3. Performance on Scales for Outcome in Parkinson's Disease-Sleep (SCOPA-S) index.

SCOPA sleep index	PwPD Median (IQR)	Controls Median (IQR)	U-test	p
A. Sleeping at night				
1. In the past month, have you had trouble falling asleep when you went to bed at night?	3 (2-4)	1 (1-2)	1656.00	<0.001*
2. In the past month, to what extent do you feel that you have woken too often?	3 (2-4)	1 (1-1)	936.00	<0.001*
3. In the past month, to what extent do you feel that you have been lying awake for too long at night?	3 (2-4)	1 (1-1)	819.00	<0.001*
4. In the past month, to what extent do you feel that you have woken up too early in the morning?	2 (1-3)	1 (1-4)	2875.50	0.001*
5. In the past month, to what extent do you feel you have had too little sleep at night?	3 (2-4)	1 (1-1)	1101.00	<0.001*
6. Overall, how well have you slept at night during the past month?	3 (2-4)	2 (2-2)	2821.50	0.001*
B. Sleeping during the day and the evening				
7. How often do you fall asleep unexpectedly either during the day or in the evening?	3 (2-3)	1 (1-2)	1722.50	<0.001*
8. How often do you fall asleep while sitting peacefully in the past 1 month?	4 (3-4)	1 (1-1)	279.00	<0.001*
9. How often do you fall asleep while watching TV or reading in the past 1 month?	1 (1-2)	1 (1-1)	3451.50	0.080
10. How often do you fall asleep while talking to someone in the past 1 month?	1 (1-2)	1 (1-1)	2652.00	<0.001*
11. Do you have trouble staying awake during the day or in the evening in the past 1 month?	1 (1-2)	1 (1-1)	2769.00	<0.001*
12. Perceive falling asleep during the day in the last 1 month as a problem?	1 (1-1)	1 (1-1)	3473.00	0.064

*Statistically significant at p-value of <0.05, X^2= Chi-square. IQR, Interquartile Range.

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Received: 15 August 2025; Accepted: 6 November 2026.

Contributions: all the authors made a substantive intellectual contribution. All the authors have read and approved the final version of the manuscript and agreed to be held accountable for all aspects of the work.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Ethics approval and consent to participate: appropriate approval was obtained from the hospital research and ethics committee before commencement of the study (NHREC/28/01/2020/AKTH/EC/2841).

Informed consent: informed consent was obtained from participants or from their legal proxies.

Patient's consent for publication: the patients gave their written consent to use their personal data for the publication of this paper and any accompanying images.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.