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Depression, sleep quality, and social isolation among people with epilepsy in Bhutan: A cross-sectional study

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Abstract

Purpose—The aim of this study was to analyze the possible contributions of seizure burden, sleep quality, and social integration to depression among people with epilepsy (PWE) in Bhutan.

Methods—Bhutan is a lower-middle-income country in Southeast Asia with a public healthcare system without neurologists. People with epilepsy were prospectively recruited from psychiatrist-run epilepsy clinics at the National Referral Hospital in the capital city of Thimphu. Adult participants with epilepsy were interviewed for clinical history, sleep quality using the Pittsburgh Sleep Quality Index, social networks using the Berkman–Syme Social Network Index, and depressive symptoms using the Patient Health Questionnaire – 9 (PHQ-9). A multivariable regression model was built to assess the relationship between depression as an outcome and the possible contributors of sleep quality, sex, and seizure in the prior month.

Results—Out of 80 participants (39 women, mean age: 29.4 years old, range: 18–56 years, 58 [73%] with a seizure in the previous month), 33% had poor sleep quality, 68% were socially isolated, 30% had a mild depressive symptom burden or more, and 18% reported suicidal ideation at the time of their interview. Women had a higher average PHQ-9 score versus men, which showed a trend towards statistical significance (5.6 versus 3.3 PHQ-9 points, $p = 0.07$), and on average met criteria for mild depression. Social integration was not significantly associated with sleep quality and had no relationship with depressive burden. There was a small positive correlation between poorer sleep quality and depressive symptoms which showed a trend towards statistical significance ($r = 0.21$, $p = 0.06$). In a multivariable regression, poor sleep quality was associated with higher depressive symptom burden, adjusting for participant sex, and having a seizure in the previous month ($p = 0.01$).

Conclusions—Our exploratory study disentangles the multilayered psychosocial burden of disease experienced by PWE in Bhutan, a lower-middle-income country with access to antiseizure medications and psychiatrists but not expert epilepsy services or human resources. Further

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investigation into the interrelationships among social isolation, poor sleep quality, depression, and seizure burden could identify preventable and remediable constituents of this burden.

Keywords

Epilepsy; Depression; Sleep; Social networks; Asia

1. Introduction

Epilepsy affects approximately 50 million people worldwide [1]. More than 80% of people with epilepsy (PWE) live in a low- or lower-middle-income country (LLMIC), even though these countries represent less than 50% of the global population [1–3]. Although PWE have access to a wide range of antiseizure medications (ASMs) in higher-income settings, a significant proportion of PWE in LLMICs continue to experience suboptimal epilepsy care [4,5].

Bhutan is a rural, landlocked LLMIC in Southeast Asia with a gross national income of 2970USDper capita in 2018 [6]. There are no neurologists in Bhutan. Adult PWE are primarily cared for by psychiatrists who run epilepsy clinics in the capital city, Thimphu [7]. In one cohort study, more than 50% of PWE in Bhutan were estimated to be receiving less than optimized care of their epilepsy [5].

Epilepsy can have a substantial impact on social life and overall health outcomes. People with epilepsy, especially in LLMICs, face stigmatization and discrimination, contributing to isolation and lower educational and occupational attainment [2,3]. In addition, PWE are prone to psychological issues like emotional distress, suicidal ideation, and higher rates of depression [2,4,8]. Social isolation and depression are significant contributors to reduced quality of life in PWE [9–11].

Another notable, but understudied, contributor to health outcomes in PWE is sleep quality [9,10]. People with epilepsy can experience sleep disturbance, comorbid sleep disorders, and daytime dysfunction as a result of seizures, adverse events from ASMs, or both [12,13]. Furthermore, a high proportion of PWE in LLMIC reports sleep problems as a symptom of their epilepsy [14]. Sleep disturbance in adults with epilepsy is associated with significantly higher rates of depression and significantly lower quality of life [10,12]. Depression and epilepsy have overlapping effects on sleep architecture – prolonged sleep latency, reduced sleep efficiency, and disrupted non-REM sleep – indicating the possibility of shared pathological mechanisms [15,16].

The interrelated effects of sleep, depression, and disease-related characteristics of epilepsy are understudied in LLMICs. As part of an overall study of epilepsy characterization in Bhutan, we conducted structured interviews on a prospective cohort of Bhutanese PWE, focused on epilepsy characteristics, sleep quality, and depressive symptom burden. Bhutan is atypical among LLMICs for its public healthcare system, including provision of older generation – and some newer generation – ASMs that are free of out of pocket costs to PWE. However, high degrees of stigma, broad use of traditional medicine approaches, and the rural and remote population make epilepsy care in Bhutan challenging [7]. Similar to

many LLMICs, epilepsy care in Bhutan is provided exclusively by nonneurologists, in this case via referral to Bhutanese psychiatrists.

The aim of the present study is to analyze the possible contributions of seizure frequency, sleep quality, and social integration to depression among PWE in Bhutan.

2. Material and methods

2.1. Ethics approval

This study was approved by the Research Ethics Board of the Ministry of Health of the Kingdom of Bhutan and the Partners Healthcare Human Research Committee in Boston, USA. All participants provided individual written informed consent, or if applicable, consent by a next of kin proxy.

2.2. Study setting and population

Bhutan is a Himalayan LLMIC with a population of 754,000 [17]. The Department of Psychiatry at the Jigme Dorji Wangchuk National Referral Hospital (JDWNRH), the only referral hospital in Bhutan, is located in the capital city of Thimphu and provides the majority of care to PWE from all districts. People with epilepsy may first present to rural health posts or “Basic Health Units” where nurses or general health practitioners are the primary providers of care, and then are referred to the Epilepsy Clinic at JDWNRH for ongoing care.

Antiseizure medications available in Bhutan include the range of older generation of ASMs, namely carbamazepine, phenytoin, phenobarbital, and valproic acid although levetiracetam and lamotrigine are also available on an individuated request basis for PWE who have had uncontrolled seizures on older generation ASMs. Antidepressant medications available in Bhutan include the tricyclic antidepressants (e.g., amitriptyline) and a selective serotonin reuptake inhibitor (fluoxetine). Patients have access to testing for thyroid-stimulating hormone (TSH) which is investigated routinely among patients endorsing depressive symptoms.

Adult patients (≥18 years) with two or more unprovoked seizures in the prior year, presenting to the JDWNRH, were prospectively recruited into this convenience cohort study.

2.3. Data collection and measures

Participants were prospectively enrolled from April 2018 to July 2019 in a consecutive manner for clinical history, sleep quality, social networks, and depressive symptoms in the form of a structured interview. Each participant was seen by at least one Bhutanese psychiatrist at the JDWNRH as part of the screening and confirmation of the diagnosis of epilepsy. One trained Bhutanese research coordinator conducted all interviews in a standardized fashion at JDWNRH.

2.3.1. Sleep quality assessment—The Pittsburgh Sleep Quality Index (PSQI) is an instrument used to measure the quality of sleep in adults. It differentiates “good” from “poor” sleep quality by assessing the following seven domains of sleep: subjective quality,

latency, duration, habitual efficiency, disturbances, use of sleep medication, and daytime dysfunction over the previous month. Scores range from0 to 21where scores ≥5 indicate "poor" sleep quality [18].

2.3.2. Social integration assessment—The Berkman–Syme Social Network Index (SNI) is a self-report questionnaire used in adults. It provides an egocentric measure of social connectedness. It uses a composite measure of the following four types of social connections: marital status, number and frequency of close contacts with relatives and friends, church group membership, and community organization membership. In Bhutan, "church group" was rephrased as "religious services" given that the vast majority of the country is Buddhist. Scores range from 0 to 4: 0 or 1 represent the most isolated category and 2–4 represent increasing social connectedness [19].

2.3.3. Depression assessment—The Patient Health Questionnaire (PHQ) is a diagnostic instrument for depression. The PHQ queries for the following nine criteria for major depression: anhedonia, depressed mood, sleep troubles, lethargy, appetite change, guilt, trouble concentrating, feeling slowed down or restless, and thoughts of suicide or self-harm. Scores range from 0 to 27 with depression severity stratified: minimal, 0–4; mild, 5–9; moderate, 10–14; moderately severe, 15–20; and severe, 20 or more [20].

2.4. Data handling and statistical analyses

Quality control on the data was performed by the Bhutanese and U.S.-based authors at the time of data collection. Data were entered into a secure database and analyzed descriptively on the variables of interest.

A complete case analysis was performed. Participants with complete data on the main variables of interest: depressive symptoms, social integration, and sleep quality were included in the final analysis. Exploratory analyses were performed and included graphically displaying the variables for distribution. Sex was explored as a variable of interest. Tests of two proportions and *t*-tests were used for comparing summary measures between two groups, i.e., depressed and nondepressed.

To analyze the relationships between sleep quality, social networks, and depressive symptoms, we conducted Pearson product moment correlation tests between PSQI and PHQ-9, PSQI and SNI, and PHQ-9 and SNI. We hypothesized that there would be a positive correlation between PSQI and PHQ-9 and negative correlations between PSQI and SNI as well as between PHQ-9 and SNI.

A multivariable regression model was then used to determine the influence of poor sleep quality on depressive symptoms after controlling for participant sex and seizure occurrence in the prior month. A p-value of <0.05 was considered statistically significant. All analyses were conducted using the statistical programming language R (Vienna, Austria) [21].

3. Results

3.1. Summary of participants

Eighty-one Bhutanese PWE were enrolled. One participant was excluded from the final analysis because of incomplete data on the main variables of interest, leaving a final sample of 80 analyzed PWE.

The average age at the time of enrollment was 29.4 years old (range: 18–56 years, 49% female). Seventy-nine participants (98.7%) were prescribed at least one ASM, and 58 (72.5%) reported experiencing a seizure in the previous month (Table 1).

3.2. Categorizations of depressive symptom burden, sleep quality, and social isolation

The depressive symptom burden, sleep quality, and social integration of adult PWE in Bhutan are provided in Table 2. Twenty-six participants (32.5%) had poor sleep quality (PSQI ≥ 5), and 54 (67.5%) were considered socially isolated (SNI < 2). Twenty-four (30.0%) were categorized with at least a mild depressive symptom burden (PHQ-9 ≥ 5), and 14 (17.5%) reported suicidal ideation. Taking an antidepressant medication was prescribed and reported by 12.5% of participants. People with epilepsy, stratified by sleep quality and depressive symptom burden scores, are enumerated in Table 3.

3.3. Exploratory analyses by sex and seizure in the prior month

The proportion of women versus men who reported social isolation and poor sleep was similar. Neither social isolation nor sleep quality differed by sex in a statistically significant way. Women had a higher average PHQ-9 score versus men which showed a trend towards statistical significance (5.6 versus 3.3 points, $p = 0.07$). This indicates that women on average met criteria for mild depressive symptom burden, while men did not.

Having a recognized seizure in the prior month did not differ between PWE who were socially isolated versus not, depressed versus not, or had poor sleep quality versus not.

3.4. Relationships between depressive symptom burden, sleep quality, and social isolation

There was no significant correlation between SNI and PSQI ($r = -0.11$, $p = 0.31$). There was no correlation observed between SNI and PHQ-9 ($r = -0.03$, $p = 0.80$). There was a small positive correlation between PSQI and PHQ-9which showed a trend towards statistical significance ($r = 0.21$, $p = 0.06$).

A multivariable regression model was constructed with depressive symptom burden as the outcome variable (Table 4). After adjusting for participant sex and seizure in the previous month, poor sleep quality was associated with higher depressive symptom burden ($p = 0.01$). In post hoc power analyses of the multilinear regression model in Table 4, with a level of significance of alpha = 0.05, the statistical power was 0.769.

4. Discussion

People with epilepsy in LLMICs face substantial psychosocial burdens. We analyzed a convenience cohort of PWE at the JDWNRH Psychiatry Department in Bhutan. Approximately two-thirds of our cohort were categorized socially isolated, and one-third met criteria for at least mild depressive symptom burden. While well above the prevalence in the general Bhutanese population without epilepsy [22], the prevalence of depression, suicidality, and social isolation in PWE in Bhutan was congruent with, or slightly below, numbers published in other LLMICs [23–26]. We do not have a control group to determine the prevalence of depression in people without epilepsy in Bhutan; however, depression is recognized to be a common condition in this country [27]. A 2018 study [28] of 120 Bhutanese adults with chronic, nonneurological medical illnesses found a similar mean PHQ-9 score (4.2 versus our sample mean of 4.4 points). Rapid urbanization has been proposed as one explanation of overall rising levels of depression in Bhutan [28].

Our analysis did not show a statistically significant correlation between social isolation and depressive symptoms. This finding was contrary to our expectation since social isolation and depressive symptoms often coexist. Several explanations can be posited but not confirmed with our data. First, SNI may not adequately measure social integration in the Bhutanese population as it has not been previously studied in the Bhutanese or similar cultural contexts. Second, more than two-thirds of our participants were classified as “socially isolated.” The gradient within the category of isolation may be important. Third, since the SNI considers the number of close contacts, but not the *level of support* they provide, the SNI may not indicate the overall level of support, a factor which is more closely linked with depression. Finally, some Bhutanese authors have posited that women who are living in rural areas with a combination of heavy farming and family responsibilities are more depressed [28,29], suggesting that PWE with fewer social ties also have fewer social pressures and therefore fewer stressors that could lead to depression.

Nor did our study find that seizure control differed by sex in Bhutan, with approximately the same proportion of women and men having a seizure in the month prior to enrollment. However, women in our cohort on average met criteria for mild depressive symptom burden, while men did not. While this was not a statistically significant finding, there may be clinically significant gender differences in the experience of epilepsy, or at least the reporting of depressive symptoms of epilepsy, in Bhutan. This finding is in line with epidemiological data that show women are twice as likely as men to experience depression [30] and may reflect a combination of biological and nonbiological factors from hormonal differences to societal expectations to understanding of one’s own symptoms [28–31].

Epilepsy has a bidirectional relationship with sleep. Poor sleep quality and sleep disturbances prevalent in PWE are associated with seizure burden. Poor sleep quality is also associated with daytime dysfunction and depression [12] and negatively impacts to quality of life [10]. Even so, there are a limited number of studies available that explore sleep quality in PWE in a LLMIC. The studies available showcase the prevalence of sleep disorders and the relationship between daytime dysfunction and quality of life [13,32]. While we found no significant correlation between social integration and sleep quality, sleep

quality and depressive symptoms had a small positive correlation that showed a trend towards statistical significance.

Our regression model demonstrated that poor sleep quality was associated with higher depressive symptom burden, adjusting for participant sex and seizure in the previous month. This finding highlights the potential importance of sleep quality on the depressive burden experienced by PWE in LLMIC. This warrants further research into how addressing poor sleep quality could serve as a therapeutic target in PWE in LLMICs more broadly. Since populations in LLMICs are less likely to have high sleep quality in general – due to a variety of circumstances such as low-wage labor pressures, noise pollution, overcrowding, unstable dwellings, and poor sanitation – the experiences of PWE in LLMICs in particular are deserving of further study [33,34].

We found that 73% of patients reported experiencing a seizure in the previous month, despite nearly every participant being prescribed ASMs. This signifies that treatments for epilepsy are available in Bhutan, but PWE still experience poorly controlled epilepsy. This finding in line with research that PWE in LLMIC could benefit from more optimized care, even when ASMs are readily available [5]. Thirty-three percent of our cohort reported not taking their medication consistently, and more than 50% of participants were prescribed only one ASM at the time of their participation.

This study has limitations. First, there is limited evidence available for the validity of the outcome scales in a population of PWE in LLMICs like Bhutan. For example, the SNI typically uses church group membership as a category of social connectedness. In Bhutan, we used the phrase “religious services”; however, other measures of social integration may be better suited to the Bhutanese population. Second, two questions on the PHQ-9 address sleep disruption and daytime dysfunction, overlapping with domains of sleep quality measured by the PSQI. This could partially explain the trend towards the significant correlation that we found between these two scores. We did not record objective measures of sleep quality, such as actigraphy or polysomnography, which are considered gold standards of sleep assessments. These are not available in Bhutan and can be expensive. Fourth, this is an observational cohort study of convenience. It is subject to referral bias, likely selecting for more severe cases of epilepsy, and may not reflect the burden of sleep disturbance, social isolation, and depression of more rural and remote areas of the country. Although we assume that more severe cases of epilepsy are referred to the capital city, severe cases of depression and PWE with the lowest educational levels may be unwilling or unable to access JDWNRH easily. Finally, by design of our study, we lack a control group. Although depression is common in Bhutan in general [27], the exact population prevalence of depression by age group, gender, and education is not well known.

5. Conclusion

Our findings provide exploratory data demonstrating the multilayered psychosocial burden of disease experienced by PWE in Bhutan, a lower-middle-income country with access to ASMs and psychiatrists but not expert epilepsy services. Further investigation into the

interrelationships among social isolation, poor sleep quality, depression, and seizure could identify remediable and preventable constituents of this burden.

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Table 1

Demographic and seizure characteristics (n = 80).

Age (years)	
Mean (standard deviation (sd))	29.4 (9.0)
Range	18-56
Sex	
Female	39 (48.8)
Highest educational level	
No schooling	13 (16.3)
Completed primary schooling	21 (26.3)
Completed secondary schooling	19 (23.8)
Completed high school	14 (17.5)
Completed college/university	13 (16.3)
Years since diagnosis	
Mean (sd)	9.3 (8.4)
Seizure burden	
Last seizure	
Within the previous week	37 (46.3)
Within the previous month	21 (26.3)
Within the previous year	19 (23.8)
Greater than one year ago	3 (3.8)
Seizure characteristics	
Loss of consciousness	76 (95.0)
Falling to ground with stiffening and shaking	53 (66.3)
Falling to ground, no shaking	3 (3.8)
Uncontrollable shaking, one part of body	3 (3.8)
Staring spells	8 (10.0)
Unusual behavior	5 (6.3)
Unusual sensory events	5 (6.3)
Seizure triggers	
Forgetting to take medication	15 (18.8)
Lack of sleep	11 (13.8)
Stress	22 (27.5)
Seizure treatment	
Number of antiseizure medications	
0	1 (1.3)
1	43 (53.8)
2	26 (32.5)
>2	10 (12.5)
Current antiseizure medication	
Phenobarbital	11 (13.9)
Phenytoin	33 (41.3)

Carbamazepine	22 (27.9)
Lamotrigine	4 (5.0)
Sodium valproate	24 (30.0)
Levetiracetam	20 (25.6)
Clonazepam	3 (3.9)
Clobazam	3 (3.9)
Diazepam	1 (1.3)
“Do you take your medication consistently?”	
Yes	54 (67.5)
No	26 (32.5)
Traditional medicine	7 (9.1)
Special diet	41 (51.3)

Table 2

Disease characteristics.

Total sample (n = 80)	
Depressive symptoms	
PHQ-9, mean (sd)	4.4 (5.6)
Depression severity	
No depression (PHQ-9 < 5)	56 (70.0)
Mild depression (PHQ-9 ≥ 5)	9 (113)
Moderate depression (PHQ-9 ≥ 10)	8 (10.0)
Moderately-severe depression (PHQ-9 ≥ 15)	6 (75)
Severe depression (PHQ-9 ≥ 20)	1 (13)
Current psychiatric medication	
Antidepressants	10 (12.5)
Sleep quality	
PSQI, mean (sd)	3.9 (25)
“Good” sleep quality (PSQI < 5)	54 (67.5)
“Poor” sleep quality (PSQI ≥ 5)	26 (325)
Social networks	
SNI, mean (sd)	1.2 (059)
Socially isolated (SNI < 2)	54 (67.5)
Socially connected (SNI ≥ 2)	26 (325)

PHQ-9: Patient Health Questionnaire - 9; PSQI: Pittsburgh Sleep Quality Index; SNI: Berkman-Syme Social Network Index.

Table 3

Sleep quality and depression severity (n = 80).

	PHQ-9 < 5 None	**PHQ-9 ≥ 5 Mild**	**PHQ-9 ≥ 10 Moderate**	**PHQ-9 ≥ 15 Moderate-severe**	**PHQ-9 ≥ 20 Severe**	**Total**
PSQI < 5 Good	40	8	2	4	0	54
PSQI ≥ 5 Poor	16	1	6	2	1	26
Total	56	9	8	6	1	80

PHQ-9: Patient Health Questionnaire - 9; PSQI: Pittsburgh Sleep Quality Index.

Table 4

Regression model: predictors of depression symptom burden.

	Estimate	Standard error	p-Value
Female sex	2.35	1.20	0.06
Seizure in previous month[a]	0.16	1.37	051
Poor sleep quality[b]	3.32	1.30	0.01

[a]Dichotomized based on one or more seizures in the last month or no seizures in the last month.

[b]Dichotomized based on PSQI score ≥ 5 equals poor sleep quality.