Neuro-Oncology Practice
8(1), 48–59, 2021 | doi:10.1093/nop/npaa057 | Advance Access date 12 September 2020

Exploring sleep disturbance among adults with primary or secondary malignant brain tumors and their caregivers

Megan S. Jeon, Haryana M. Dhillon, Eng-Siew Koh, Anna K. Nowak, Elizabeth Hovey, Joseph Descallar, Lisa Miller, Nathaniel S. Marshall, and Meera R. Agar

South Western Sydney Clinical School, University of New South Wales, Sydney, Australia (M.S.J., E.S.K., J.D., M.R.A.); Centre for Medical Psychology & Evidence-based Decision-making, University of Sydney, Sydney, Australia (H.M.D.); Ingham Institute for Applied Medical Research, Liverpool, Australia (E.S.K., J.D., M.R.A.); Department of Radiation Oncology, Liverpool Hospital, Liverpool, NSW, Australia (E.S.K.); Medical School, QEII Medical Centre Unit, University of Western Australia, Crawley, Australia (A.K.N.), Department of Medical Oncology, Sir Charles Gairdner Hospital, Nedlands WA, Australia (A.K.N.); Nelune Comprehensive Cancer Centre, Prince of Wales Hospital, Randwick, Australia (E.H.); University of New South Wales, Sydney, Australia (E.H.); Sir Charles Gairdner Hospital, Perth, Australia (L.M.); Woolcock Institute for Medical Research & Sydney Nursing School, University of Sydney, Sydney, Australia (N.S.M.); IMPACCT (Improving Palliative, Aged and Chronic Care through Clinical Research and Translation), Faculty of Health, University of Technology Sydney, Sydney, Australia (M.R.A.)

Corresponding Author: Megan S. Jeon, BPsych (Hon), Ingham Institute for Applied Medical Research, 1 Campbell St, Liverpool, NSW, 2170, Australia (m.jeon@student.unsw.edu.au).

Abstract

Background. Emerging evidence supports the clinical impact of sleep disturbance (SD) on cancer patients. This study aimed to determine the prevalence and predictors of SD in people with malignant brain tumors and caregivers, and explore any relationship between the patient-caregiver dyad's sleep.

Methods. Eighty-one adults with primary malignant (91%) or metastatic (9%) brain tumors and their family caregivers (n = 44) completed a series of self-report questionnaires, including the Pittsburgh Sleep Quality Index (PSQI), the Insomnia Severity Index, and the drowsiness item of The MD Anderson Symptom Inventory-Brain Tumor in an Australian ambulatory neuro-oncology setting. Participants were grouped by the PSQI cutoff (SD > 5), and binary logistic regression analyses were performed to identify risk factors.

Results. Of patients, 53% reported SD and 15% of those clinically significant insomnia, and 27% reported moderate to severe daytime drowsiness. Whereas anxiety, depression, fatigue, pain, neurocognitive symptoms, and antiemetic use were higher in patients with SD, fatigue and KPS were strong predictors of SD. In caregivers, 55% reported poor sleep and 13% clinical insomnia. Anxiety, caregiver burden, and comorbid illness were significantly associated with caregivers' SD. The individual's SD did not affect the chance of the other member of the patient-caregiver dyad experiencing SD.

Conclusions. More than half the sample had sleep disturbance, which was linked to many concomitant symptoms, such as fatigue in patients and anxiety in caregivers, potentially contributing to distress and functional impairment. Understanding underlying mechanisms of SD, the potential use of these clinical predictors in care settings, and options for management is warranted.

Keywords

brain tumor | caregiver | glioma | sleep disturbance | supportive care

Sleep disturbance is a general term referring to subjectively perceived or actual disturbance to sleep-wake patterns, quantity, or quality that results in excessive daytime somnolence and functional impairment.[1] In clinical populations, those with cancer and neurological diseases, sleep disturbance can manifest as insomnia and somnolence.[2] The prevalence of sleep disturbance in various cancer types ranges between 30% and 50%;[3] however, some report figures as high as 85% in advanced cancer.[4,5] Although they may not meet criteria for a formal diagnosis of sleep disorders, many people with cancer are affected by disrupted sleep.[6]

Despite the increasing incidence of brain tumors (particularly brain metastases), the prevalence of sleep disturbance in brain tumor (BT) patients has had little exploration. Sleep disturbance was reported in 47% of 340 recurrent glioma patients in a retrospective chart review,[7] and around 80% in people with brain metastasis undergoing whole-brain radiation therapy.[8] Also, excessive drowsiness and sleep disturbance, alongside fatigue, are the most commonly reported symptoms in people with malignant BT.[9] Sleep disturbance frequently appeared in clusters of highly intercorrelated symptoms including fatigue, depression, anxiety, pain, or cognitive impairment in people with high-grade and metastatic BT,[10–12] and all can adversely affect health-related quality of life (HRQoL), adherence to cancer treatment, and prognosis.[8,13–15] Sleep disturbances can occur at any point during the BT trajectory.[9] Despite these clinical implications, much of the available evidence is from the general cancer populations or limited to describing the presence of sleep disturbance as part of the HRQoL outcomes of patients with BT across different treatment regimens.[9] A strong evidence base for the prevalence, type, and risk factors of sleep disturbance in people with brain cancer is lacking.

Caregivers of people with cancer commonly experience sleep disturbance along with fatigue, depression, and anxiety, although they seldom seek help for this symptom.[16] Symptoms of caregiving stress manifest as psychological distress, including anxiety, depression, worry, and loneliness.[17] Higher levels of emotional distress are associated with increased sleep disturbance, fatigue, and unhealthy behavior.[16] Despite this, few studies have addressed sleep disturbances and their impact on caregivers of patients with advanced cancers[18] or primary BT.[19] The caregivers' role in the support and management of the BT illness and treatment schedules present unique caregiver strain. Cognitive deterioration, personality change, disinhibition, communication difficulties, and keeping a meaningful relationship with the patient are all devastating challenges caregivers of BT patients cope with, making caregiving difficult and demanding.[20]

This study aimed to explore the sleep patterns and prevalence of sleep disturbance in community-dwelling patients with primary malignant or secondary BT and their family caregivers. Secondary objectives were to investigate risk factors for sleep disturbance in patients and caregivers and the relationship between the patient and caregiver dyad's sleep. We hypothesized that sleep disturbance would be prevalent both in patients and caregivers, and the dyad's sleep patterns and disturbance would be closely related.

Methods

Participants were recruited from 4 outpatient cancer centers in Sydney and Perth, Australia, from November 2015 to March 2018, receiving most primary or secondary BT referrals residing in these geographic areas. Ethical approval was obtained for all sites. The study is a prospective, cross-sectional design to describe sleep patterns and disturbances in BT patients at various points of the disease trajectory, and their caregivers. Eligible patients were ambulatory outpatients age 18 years or older, with a confirmed diagnosis of primary malignant or metastatic brain neoplasm, and able to provide written consent and undertake study measures independently in English. Eligible caregivers were individuals identified by an eligible patient as their primary caregiver, age 18 years or older, with no language or self-reported health constraints on providing written consent and completing study measures. Patients and caregivers both could participate in a dyad (patient and caregiver) or alone, and when the caregiver participated alone the required demographic and clinical information of the patient was obtained with consent of the patient. Eligible participants were initially briefed about the study during their consultation with a medical or radiation oncologist, with the researcher subsequently explaining the study requirements and obtaining informed consent. Participants completed the booklet of questionnaires at the clinic or at home and returned it to the researcher in person or via mail.

Study Tools

Sleep assessment tools for all participants

The Pittsburgh Sleep Quality Index (PSQI)[21] is a 19-item self-report measure of sleep quantity and quality, adapted for a 1-week recall interval in the present study (as per previous research[22,23]). The PSQI yields 7 component scores: subjective sleep quality, sleep latency (time taken to fall asleep), duration, habitual sleep efficiency (percentage of time in bed asleep), sleep disturbances (eg, nocturnal urination, snoring, feeling too hot or pain), use of sleeping medication, and daytime dysfunction. Each component score is rated on a 0 to 3 scale, and the global score summing all component scores ranges from 0 to 21, with a higher score suggesting poorer sleep quality. A cutoff score of greater than 5 yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% for detecting poor sleepers in clinical samples.[21] In the context of cancer, the PSQI has demonstrated internal consistency (Cronbach α of .80 across multiple cancer groups) and construct validity.[22]

The Insomnia Severity Index (ISI)[24] is a self-report measure of insomnia over a 2-week time interval. It consists of 7 items on a 0 to 4 scale, and the total score ranges from 0 to 28. In general, scores 8 to 14 indicate subthreshold insomnia, 15 to 21 indicate clinical insomnia of moderate severity, and 22 to 28 indicates clinical insomnia of high severity. The ISI comprises 4 sleep-related items assessing the severity of sleep onset and maintenance difficulties, and satisfaction with current sleep

pattern, and 3 wake-related items assessing impairment of daily functioning, noticeability of insomnia-induced impairment, and degree of distress or worry caused by the sleep problem.[25] The ISI has demonstrated its validity and excellent internal consistency (overall Cronbach α of .90) in cancer samples.[26]

Patient questionnaire booklet

The patient questionnaire booklet comprised the sleep survey, the PSQI, the ISI, the Hospital Depression and Anxiety Scale (HADS),[27] the Brief Pain Inventory—Short Form (BPI-SF),[28] the Modified Brief Fatigue Inventory (MBFI),[29] and The MD Anderson Symptom Inventory—Brain Tumor (MDASI-BT).[30] Demographic and clinical information were collected from the medical record and included sex, age, marital status, smoking status, alcohol consumption, BMI, tumor type and characteristics, treatment history, and current medications. The clinician survey collected information on KPS, the presence of a preexisting psychological disorder, delirium, and a range of symptoms and medical conditions common to BT that may interrupt sleep. The sleep survey included the history of sleep disturbance before the diagnosis of BT, known diagnosis of sleep disorder, the current status of a preexisting sleep condition, history of sleep disturbance of family, the presence of a sleep partner, and perception of the sleep environment. The HADS is a validated measure of the level of depression and anxiety for use in general and medical settings,[31] including cancer populations.[32] A score of 8 or more indicates at least mild anxiety and depression.[31] The BPI-SF assessed the severity of pain and functional interference on a scale 0 to 10, with higher score indicating more severe pain. The MBFI assesses fatigue severity and fatigue-induced interference on a 1 to 7 scale, with a higher score indicating more severe fatigue. The MDASI assessed a set of common BT-related symptoms (13 core and 9 BT items) of physical, cognitive, and psychological domains as well as their functional interference (6 items) on a 0 to 10 scale, with a higher score indicating higher level of symptom severity or interference. Drowsiness (feeling sleepy) and neurocognitive deficits, including weakness on one side of the body, difficulty speaking, difficulty understanding, and difficulty remembering, were assessed by the MDASI-BT.

Caregiver questionnaire booklet

The caregiver questionnaire booklet comprised the demographics and caregiver survey, the PSQI, the ISI, the HADS, the EuroQol Five Dimension Questionnaire (EQ-5D),[33] the Caregiver Quality of Life Index–Cancer (CQOLC),[34] and the Activities of Daily Living scale (ADL).[35] The demographics and caregiver survey included sex, age, marital status, relationship with the patient, employment, medical condition, medications, and caregiving factors, including the total weekly care hour (0-168 hours), duration of the caregiver role, other caregiver roles, communication difficulty, and night-time care needs. The PSQI, ISI, and HADS were as described previously. The EQ-5D assesses the caregiver's general health status in mobility and pain on a scale of 1 (no problem) to 5 (nonfunctional or severe problem) and one visual analog scale ranging from 0 to 100 for the current health level, with higher scores indicating better health. The CQOLC is validated for use in caregivers of cancer patients to assess the level of caregiver burden, disruptiveness to daily or social life, financial concerns, and quality of life (QoL). It consists of 35 items on a 0 to 4 numeric scale, with a higher score indicating higher caregiver burden and distress. The ADL was used to assess the level of patient's dependency on caregivers in performing 9 daily activities on a 0 (independent) to 3 (dependent) scale.

Statistical Analysis

Descriptive statistics were computed for participant characteristics, scores of study measures, and sleep parameters, including bedtime at night, wake time, total sleep time, sleep latency, and sleep efficiency ($\frac{\text{Total Sleep Time}}{\text{Dif ference between bedtime and wake time}} \times 100$, %) using the PSQI questions 1 to 4. The prevalence of sleep disturbance and clinically significant insomnia were computed using the established cutoff scores (PSQI global > 5 and ISI ≥ 15). Mean (standard deviation) of the MDASI-BT drowsiness (feeling sleepy) and percentage of moderate to severe drowsiness (scores ≥ 5)[2] were computed for patients.

Participants were assigned to a high sleep disturbance (HSD) group or a low sleep disturbance (LSD) group by the PSQI cutoff. Descriptive statistics for sleep parameters (bedtime, wake time in the morning, sleep latency, total sleep time, and sleep efficiency) and sleep outcomes (PSQI components and global scores, ISI, and MDASI drowsiness scores) were reported by the groups. Group differences in the sleep parameters and drowsiness score were compared using one-way analysis of variance, except for PSQI components and global and ISI scores. Other study variables (continuous), and group differences in individual variables were computed.

For patients, differences between the sleep disturbance groups on demographic and clinical variables, history of sleep disturbance before diagnosis, and current medications (chemotherapy, corticosteroids, antiemetics—not including steroids, and anticonvulsants) were assessed using Fisher exact test for categorical variables and Mann-Whitney *U* test for continuous variables. Similarly, group differences of caregivers were tested using Fisher exact and Mann-Whitney *U* test on demographic, health, and caregiver variables.

The secondary outcome was to determine risk factors for sleep disturbance. Patient study variables hypothesized as risk factors for sleep disturbance included depression, anxiety, fatigue, pain, and neurocognitive disturbance (MDASI-BT items of weakness on one side of the body, difficulty speaking, difficulty understanding, and difficulty remembering). Caregiver study variables included depression, anxiety, health (mobility, pain, and general health status), caregiver QoL items, and level of patient dependency (ADL). Univariate binary logistic regression models were computed for individual variables. For multivariable analysis, forward stepwise binary logistic regression models were computed to determine risk factors for patients' sleep disturbance. Demographic and clinical variables associated with sleep disturbance at *P* less than .05

were considered candidate variables in the regression. Multivariable analysis was not performed for caregivers' sleep disturbance because of small sample size.

Pearson correlation coefficients were computed to determine associations between the patient and caregiver dyad's sleep patterns and parameters. Fisher exact test was used to examine the association between patient and caregiver for the presence of sleep disturbance. All statistical analyses were performed using the SPSS software (2015, IBM Corp) and the significance (α) level of .05.

Results

Participant Characteristics

Patient participants' characteristics are presented in Table 1, and caregiver characteristics in Table 2. Eighty-one patients diagnosed with primary (91%) or metastatic (9%) BT and 44 caregivers completed the study (37 patients participating alone and 44 patient-caregiver dyads). All caregivers were a family member of the patient (referred to as "caregiver"). The majority of patients were male (62%), married (79%), and had KPS of 90 or higher (74%). The mean age was 51 years (SD = 14.3). Of patients with primary BT (n = 74), 73% had high-grade tumors with 51% glioblastoma. Patients were primarily treated with surgery (93%), and 35 patients (43%) were on chemotherapy. Caregivers were primarily female (75%), married (96%), and spouses of patients (89%) with a mean age of 53 years (SD = 13.3).

Sleep Outcomes

The majority of patients had a sleep partner (65%). Interestingly, 45% of patients were not content with the sleep environment, finding external factors including lighting, noise, or temperature bothersome for sleeping. Twenty-four (31%) patients self-reported having sleep disturbance before diagnosis, including sleep apnea (n = 4) and restless leg syndrome (n = 1), but predominantly general sleep disturbance not meeting diagnostic criteria for a sleep disorder (n = 12) or secondary to anxiety or headache (n = 5). Two people worked as shift workers. Of these 24, 50% had not sought treatment for preexisting sleep disturbance, and the condition was current. Twenty-two patients (28%) had a family member with a known sleep disorder.

The main sleep outcomes are presented in Table 3, including sleep parameters, PSQI component and global scores, ISI, and MDASI-BT drowsiness (patient only) by sleep disturbance groups. In patients, using the PSQI cutoff, 53% (n = 41) of patients had a sleep disturbance (HSD), and the ISI identified 15% (n = 12) as having moderate clinical insomnia. Mean (SD) drowsiness score was 2.95 (2.72), and moderate to severe drowsiness was reported in 27% (n = 22) of patients. Patients with HSD felt significantly more drowsy (M = 3.85 vs 2.09, $P = .004$), had longer sleep latency (M = 32.7 minutes vs 11.1 minutes, $P = .004$), shorter total sleep time (M = 6.1 hours vs 8.3 hours, $P < .001$), and lower sleep efficiency (M = 69% vs 93%, $P < .001$) compared to patients in the LSD group. Bedtime at night and wake time in the morning were comparable across the SD

Table 1. Demographic and Clinical Characteristics of Patient Participants

Demographic variables	All patients (n = 81)
Age, mean (SD), y	51.1 (14.3)
Sex (male), n (%)	50 (62)
Marital status (married), n (%)	64 (79)
KPS, n (%), %	
100	38 (47)
90	22 (27)
≤ 80	21 (26)
BMI, mean (SD)	26.9 (5.4)
Smoking, n (%)	
Current	5 (6)
Previous	27 (33)
Never	30 (37)
Alcohol consumption (regular/occasional), n (%)	36 (44)
Clinical variables	**All patients (n = 81)**
Brain tumor type, n (%)	
Primary	74 (91)
Grade IV	39 (53)
Grade III	15 (20)
Grade II	17 (23)
Other	3 (4)
Metastatic	7 (9)
Primary site (lung/breast)	4 (57)
Brain lesions (≥ 2)	6 (86)
Location, n (%)	
Frontal	23 (28)
Temporal	20 (25)
Parietal	13 (16)
Occipital	2 (3)
Multiple	17 (21)
Other	6 (7)
Laterality, n (%)	
Left	39 (49)
Right	31 (39)
Bilateral	10 (13)
Midline	1 (1)
Time since diagnosis, median (range), mo	12 (1-383)
Recurrence, n (%)	21 (26)
Progression in past 2 mo, n (%)	12 (15)
Treatment history, n (%)	
Surgery	75 (93)
Biopsy only	9 (11)
Radiation	37 (46)
Chemotherapy	49 (61)
Radiation with concurrent chemotherapy	50 (62)
Other	4 (5)

Table 1. Continued

Demographic variables	All patients (n = 81)
No. of symptoms reported by clinician, n (%)	
0	50 (62)
1	16 (20)
2	8 (10)
3+	7 (9)
History of psychological disorders	7 (9)
Type of common symptoms, n (%, of those presenting symptoms, n = 31)	
Lethargy	11 (36)
Headache	9 (29)
Mood disturbance	6 (19)
Nocturnal urinary and neurological deficits	5 (16)
Involuntary movement	4 (13)
Medications	**All patients (n = 81)**
Medication for complications related to cancer, n (%)	
Anticonvulsant	44 (54)
Antiemetic	29 (36)
Chemotherapy	35 (43)
Corticosteroid	20 (25)
Antidepressant	5 (6)
Benzodiazepine	8 (10)
PPI	12 (15)
Medication for comorbid illness, n (%)	21 (26)

Table 2. Caregiver Demographic Information and Caregiving Factors

Variables	All caregivers (n = 44)
Age, mean (SD), y	52.7 (13.3)
Sex (female), n (%)	33 (75)
Marital status (married), n (%)	42 (96)
Employment (working), n (%)	19 (43)
Change in employment due to caregiving, n (%)	
Decreased workload/on leave/retired	17 (41)
No change	9 (21)
Care relationship (spouse), n (%)	39 (89)
Weekly care, mean (SD), h	85.7 (69.0)
Care duration, median (range), mo	12 (2–192)
Other care duty (dependent children/elderly relatives), n (%)	21 (48)
Medical condition[a], n (%)	22 (50)
Hypercholesterolemia	9 (41)
Arthritis	7 (32)
Thyroid disorders	4 (18)
Breast cancer	2 (9)
Medication use (yes), n (%)	20 (46)

[a]Multiple responses allowed.

groups. In caregivers, 55% (n = 24) had sleep disturbance, and 13% (n = 6) moderate to severe clinical insomnia. Similar to patients, caregivers in HSD had significantly longer sleep latency (M = 34.54 minutes vs 13.35 minutes), shorter total sleep time (M = 5.71 hours vs 7.66 hours), and more reduced sleep efficiency (M = 69.79% vs 95.03%) compared to those with LSD (all $P < .001$). Bedtime at night (LSD: M = 22:13 vs HSD: 22.35, $P = .35$) and wake time in the morning (M = 06:29 vs 07:00, $P = .11$) were not significantly different between groups.

Associated Variables of Sleep Disturbance in Patients

Among demographic and clinical variables, patients on antiemetics (n = 28) were more likely to experience HSD (71%) than LSD ($P = .018$). Lower KPS (≤ 80 or > 80) was also significantly associated with HSD (79% in HSD, $P = .014$). Those with a preexisting sleep disturbance (71% in HSD, $P = .034$) or who were not content with their sleep environment (68% in HSD, $P = .019$) had a significantly higher likelihood of sleep disturbance. No other demographic or clinical variables were significantly associated with sleep disturbance.

Table 4 reports group means of study variables and results of logistic regression analyses for risk factors for sleep disturbance in patients. Univariate models showed that increased depression (odds ratio [OR] = 1.16), anxiety (OR = 1.17), pain (OR = 1.39), fatigue (OR = 1.76), weakness on one side of the body (OR = 1.42), and difficulty remembering (OR = 1.20) were implicated in sleep disturbance in patients. However, multivariable logistic regression models, including the previously mentioned clinical demographic covariates, yielded fatigue severity (OR = 1.92) and KPS (OR = 6.20) as the only significant risk factors for sleep disturbance in patients.

Associated Variables of Sleep Disturbance in Caregivers

Group means of caregiver study outcomes and univariate binary logistic regression analysis results are presented in Table 5.

Among caregiving variables, longer weekly care hours were associated with more severe sleep disturbance in caregivers (OR = 1.01). Caregivers with comorbid illness (77% in HSD, OR = 7.29) or using any medications (OR = 5.63) were more likely to have sleep disturbance.

Increased levels of anxiety (OR = 1.33), stress (OR = 2.46), sadness (OR = 2.12), mental strain (OR = 2.33), and overall caregiver burden (CQOLC total, OR = 1.03) individually significantly increased the chance of caregivers having sleep disturbance.

Associations of Patient-Caregiver Dyad's Sleep

Most caregivers slept with patients in the same bed (75%). Five (11%) provided night-time care for one or more nights

Table 3. Sleep Parameters and Outcomes by Sleep Disturbance Groups

	Patient (n = 77)		Caregiver (n = 44)	
PSQI	LSD (≤ 5)	HSD (> 5)	LSD (≤ 5)	HSD (> 5)
N (%)	36 (47)	41 (53)	20 (45)	24 (55)
Sleep parameter	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Bedtime, hh:mm	21:57 (01:09)	22:05 (01:15)	22:13 (01:12)	22:35 (01:17)
Wake time, hh:mm	06:59 (01:21)	07:00 (01:23)	06:29 (00:56)	07:00 (01:04)
Sleep latency, min	11.07 (8.57)	32.71(34.00)	13.35 (9.37)	34.54 (21.53)
Total sleep time, h	8.32 (1.21)	6.11 (1.38)	7.66 (0.71)	5.71 (1.08)
Sleep efficiency, %	92.61 (7.57)	69.20 (15.22)	95.03 (11.58)	69.79 (16.85)
PSQI components				
Sleep quality	0.47 (0.51)	1.39 (0.74)	0.75 (0.44)	1.50 (0.59)
Sleep latency	0.25 (0.44)	1.63 (1.09)	0.65 (0.75)	2.08 (0.93)
Sleep duration	0.11 (0.32)	1.17 (1.07)	0.10 (0.31)	1.54 (0.93)
Habitual sleep efficiency	0.22 (0.49)	1.80 (0.98)	0.20 (0.41)	1.79 (1.10)
Sleep disturbances	1.11 (0.47)	1.61 (0.67)	1.05 (0.41)	1.58 (0.50)
Use of sleeping medication	0.03 (0.17)	0.73 (1.23)	0.00 (0.00)	0.83 (1.27)
Daytime dysfunction	0.58 (0.69)	1.17 (0.83)	0.70 (0.47)	1.13 (0.74)
Global	2.78 (1.40)	9.51 (2.95)	3.47 (1.12)	10.46 (2.83)
ISI total	4.64 (4.39)	11.32 (4.77)	5.05 (4.57)	11.83 (4.65)
MDASI-BT drowsiness	2.09 (2.48)	3.85 (2.72)	–	–
Insomnia, n (%)	All patients (n = 81)		All caregivers (n = 44)	
None	35 (43)		17 (39)	
Subthreshold insomnia	34 (42)		21 (48)	
Moderate insomnia	12 (15)		5 (11)	
Severe insomnia	0 (0)		1 (2)	
Drowsiness, n (%)	All patients (n = 81)			
None to mild drowsiness	59 (73)			
Moderate to severe drowsiness	22 (27)			

Abbreviations: HSD, high sleep disturbance; ISI, Insomnia Severity Index; LSD, low sleep disturbance; MDASI-BT, The MD Anderson Symptom Inventory-Brain Tumor; PSQI, Pittsburgh Sleep Quality Index; TST, total sleep time.

per week. Providing companionship while the patient was awake was the most common type of nocturnal care (n = 11). The patient's bedtime at night positively correlated with the caregiver's bedtime ($r = 0.54$) and wake time in the morning ($r = 0.31$). The patient's wake time in the morning positively correlated with the caregiver's bedtime ($r = 0.49$), ISI score ($r = 0.36$) and PSQI sleep disturbance component score ($r = 0.40$).

The patient's sleep efficiency positively correlated with the caregiver's total sleep time ($r = 0.36$) but negatively with the caregiver's PSQI sleep quality component ($r = –0.32$). Increased sleep efficiency of the patient was correlated with increased total sleep time and better overall sleep quality for the caregiver.

Sleep disturbance group allocations for the dyads, as shown in Table 6, indicated the likelihood of the dyad to have sleep disturbance was not significantly different whether the patient or caregiver had sleep disturbance ($P = .21$).

Discussion

Our findings demonstrate that more than half the patients and caregivers experienced sleep disturbance. The type of sleep disturbance in this sample was largely insomnia, characterized by greater difficulty falling asleep (longer sleep latency) and thus poorer sleep efficiency, as around 60% of patients and caregivers had at least subthreshold insomnia. Given reported sleep patterns of patients and caregivers, it is possible their circadian rhythms are intact, although further research investigating this is needed. Nearly one-third of patients also experienced moderate to severe drowsiness, consistent with the previous reporting in primary BTs.[2] Sleep disturbance and daytime drowsiness have been implicated in reduced functioning and poorer QoL in BT populations.[8] It is noteworthy that one-third of patients reported preexisting sleep disturbances or disorders, which for the majority remained current

Table 4. Scores on Study Variables and Risk Factor Analysis for Patient Participants

		LSD (n = 36)		HSD (n = 41)	Univariate			Multivariable[a]		
Variable		Mean (SD)		Mean (SD)	OR	95% CI	*P*	OR	95% CI	*P*
HADS Depression		3.97 (3.27)		5.80 (3.83)	1.16	(1.01-1.33)	.032			
HADS Anxiety		4.78 (3.87)		6.98 (3.64)	1.17	(1.03-1.34)	.016			
BPI pain severity		0.92 (1.89)		2.13 (2.10)	1.39	(1.07-1.82)	.015			
MBFI fatigue severity		2.83 (1.48)		3.98 (1.35)	1.76	(1.24-2.50)	.002	1.92	(1.28-2.88)	.002
MDASI-BT										
Weakness on one side of body		0.60 (1.22)		2.07 (2.90)	1.42	(1.07-1.88)	.015			
Difficulty speaking		2.03 (2.46)		2.54 (2.00)						
Difficulty understanding		1.46 (2.12)		1.73 (1.83)						
Difficulty remembering		2.63 (3.01)		4.00 (2.57)	1.20	(1.01-1.42)	.039			
		N (%)		N (%)						
KPS	≤ 80	4 (5)	15 (20)	4.62	(1.37-15.61)	0.014	6.20	(1.44-26.59)	.014	
	> 80	32 (42)	26 (34)							
Antiemetics	Yes	8 (10)	20 (26)	3.33	(1.23-9.03)	0.018				
	No	28 (36)	21 (27)							
Preexisting sleep disturbance	Yes	7 (10)	17 (23)	3.09	(1.09-8.77)	0.034				
	No	28 (38)	22 (30)							
Perception of sleep environment	Bothered	11 (15)	23 (31)	3.14	(1.20-8.17)	0.019				
	Content	24 (32)	16 (22)							

Abbreviations: BPI, Brief Pain Inventory; HADS, Hospital Depression and Anxiety Scale; HSD, high sleep disturbance; LSD, low sleep disturbance; MBFI, Modified Brief Fatigue Inventory; MDASI-BT, The MD Anderson Symptom Inventory—Brain Tumor; OR, odds ratio.
Only significant results are presented for univariate analyses.
[a]Multivariable binary logistic regression model with MBFI fatigue severity and KPS dichotomized to greater than 80 and 80 or less.

Table 5. Scores on Study Variables and Risk Factor Analysis for Caregiver Participants

Variable		LSD (n = 20) Mean (SD)	HSD (n = 24) Mean (SD)	Univariate OR	95% CI	*P*
HADS Depression		5.00 (3.95)	5.29 (2.85)			
HADS Anxiety		5.90 (3.32)	10.46 (4.62)	1.33	(1.10-1.62)	0.004
EQ-5D Mobility		1.15 (0.37)	1.25 (0.61)			
EQ-5D Pain		1.45 (0.69)	1.71 (0.55)			
EQ-5D Health VAS		82.15 (13.07)	76.25 (15.90)			
CQOLC Level of stress		1.85 (1.27)	3.08 (1.01)	2.46	(1.35-4.50)	0.003
CQOLC Outlook on life		2.50 (1.70)	3.17 (1.37)			
CQOLC Sadness		1.20 (1.11)	2.42 (1.38)	2.12	(1.23-3.64)	0.007
CQOLC Mental strain		1.75 (1.15)	2.42 (1.21)	2.33	(1.30-4.17)	0.005
CQOLC Frustration		1.70 (1.26)	2.04 (1.16)			
CQOLC Social support		1.75 (1.33)	1.79 (1.38)			
CQOLC Relationship with patient		2.05 (1.70)	1.38 (1.53)			
CQOLC Informed about illness		2.70 (1.38)	2.88 (1.45)			
CQOLC total		48.45 (26.93)	63.12 (17.96)	1.03	(1.00-1.06)	0.045
ADL		0.15 (0.37)	1.46 (3.60)			
		Median (range)	Median (range)			
Weekly care, h		29 (2-168)	150 (2-168)	1.01	(1.00-1.02)	0.038
		N (%)	N (%)			
Medication use (n = 43)	Yes	5 (12)	15 (35)	5.63	(1.49-21.20)	0.011
	No	15 (35)	8 (19)			
Comorbid illness	Yes	5 (11)	17 (39)	7.29	(1.91-27.86)	0.004
	No	15 (34)	7 (16)			

Abbreviations: ADL, activities of daily living; CQOLC, Caregiver Quality of Life Index–Cancer; EQ-5D, EuroQol Five Dimension Questionnaire; HADS, Hospital Depression and Anxiety Scale; HSD, high sleep disturbance; LSD, low sleep disturbance; OR, odds ratio; VAS, visual analog scale. Only significant results are presented for univariate analyses. Multivariable analysis was not performed because of small sample size.

Table 6. Dyad's Sleep Disturbance Group Allocations by Pittsburgh Sleep Quality Index

		Patient LSD	Patient HSD	Total
Caregiver	LSD, n (%)	11 (61)	7 (39)	18 (44)
	HSD, n (%)	9 (39)	14 (61)	23 (56)
	Total, n (%)	20 (49)	21 (51)	41 (100)

Percentage reflects row percentage.
Abbreviations: HSD, high sleep disturbance; LSD, low sleep disturbance.

and untreated. However, this figure is comparable to the reported prevalence of sleep disturbance in the general Australian population,[36] and preexisting sleep conditions did not predict sleep disturbance in our sample, indicating the greater impact of concomitant symptoms on sleep disturbance. We found a moderate correlation between the patient's sleep efficiency and longer sleep hours and sleep quality of the caregiver. However, the likelihood of having sleep disturbance for the patient-caregiver dyad was not associated. This may be due to a considerable proportion of caregivers who developed sleep disturbance despite the patient not experiencing sleep disturbance (39% of those caregivers had HSD).

Fatigue Comorbid With Sleep Disturbance

The risk for sleep disturbance was greater for patients with more severe fatigue and poorer functional status (KPS ≤ 80), consistent with the literature.[7,12,15] Fatigue causes the greatest symptom distress and often occurs in symptom clusters with sleep disturbance and drowsiness, as reported by people with BT ranging from benign tumors to high-grade gliomas.[9] Recurrent tumor and brain radiation may be associated with worse fatigue.[2,12] Fatigue is also associated with poorer QoL and functional status, more drowsiness, and impaired physical functioning, limiting maintenance of a normal lifestyle.[37] The relationship between fatigue and sleep disturbance may be multifaceted, beyond a vicious cycle of less physical activity due to fatigue and worsening insomnia.[14] A potential mechanism underlying the fatigue-sleep cluster is neuroinflammation

induced by brain irradiation disrupting the central molecular clock, the suprachiasmatic nuclei, and altering levels of cytokines and neurotransmitters, leading to an altered sleep-wake cycle and excessive daytime drowsiness and fatigue.[13] Dysfunction in the hypothalamic-pituitary-adrenal axis and disrupted melatonin and hypocretin secretions have been implicated in the damage to the suprachiasmatic nuclei in pediatric brain tumors.[38] This neuroinflammation model proposes that increased secretion of interleukin-1 and interleukin-6 may lead to stimulation of the hypothalamic-pituitary-adrenal axis and aberrant production of melatonin, affecting arousal and circadian rhythms.[39] Recent preliminary evidence from an in vitro model of human glioblastoma cells has demonstrated a potential association between circadian rhythms of these cells and radiation therapy.[40] However, deeper investigation of the biological basis of this symptom cluster is needed.

Demographic and Clinical Variables Were not Associated With Sleep Parameters

Demographical and clinical variables were not associated with sleep disturbance in people with BT in this study. Although those with sleep disturbance were more likely to use antiemetics, neither treatment nor medications significantly predicted patient sleep disturbance. There is mixed evidence regarding the association between sleep disturbance and BT characteristics and treatment regimens.[9] Corticosteroid use has been associated with insomnia,[41] and anticonvulsant agents may contribute to excessive drowsiness.[42] Our sample had relatively good functional status (74% with KSP 90-100), and few patients remained on corticosteroids, even fewer on high doses, although demographics are similar to previous larger studies.[2,41] Patients on antiemetics may experience nausea and/or receive nausea-inducing anticancer treatment, which can induce feelings of sickness and contribute to sleep disturbance. We could not determine the relative effect (or mediating role) of antiemetics with the extent of the current data. Further research with larger sample sizes is warranted because of the multitude of medications used in people with BT to assess subtle but clinically important effects of different medications.

Caregivers' Anxiety and Burden May Impair Sleep

Family caregivers in this study had high levels of anxiety, stress, sadness, mental strain, and caregiver burden, which were all associated with sleep disturbance. Having existing health conditions, mostly hypercholesterolemia and arthritis, and longer hours of care per week significantly increased caregivers' chance of developing sleep disturbance. These results substantiate previous findings in caregivers of people with advanced cancer and malignant BT. Poor sleep quality or sleep disturbance was reported in 30% to 72% of caregivers.[18,19,43] Longer sleep latency, high fragmentation (frequent waking after sleep onset), and movement during sleep were common, and caregivers frequently required daytime naps.[18,19,43] Strong correlations have been found between anxiety, caring burden, and sleep disturbance in caregivers.[18,19] Even when objective measures of sleep suggested marginal impairment, caregivers who were more anxious or psychologically distressed reported poor sleep.[43] Family caregiving is a complex biopsychosocial process, complicated by multiple competing priorities.[16,44] Caregivers of those with high-grade gliomas described caregiving as an ambiguous, relentless, exhausting task where dealing with cognitive impairment and personality change in the patient was most challenging.[20] Symptoms of excessive caregiver burden may include high levels of anxiety, depression, worry, and extreme loneliness.[16] Caregivers have limited time for self-care, often postpone their own health care needs, and rarely seek external supports.[16,20] Indeed, in this study, caregivers spent on average more than 85 hours per week (12 hours daily) caregiving, considerably longer than the time reported by other cancer caregivers (40 hours per week[16]). The lack of relaxation time for caregivers warrants clinical attention given a potential mechanism of excessive burden leading to disrupted stress response and impaired sleep-wake rhythms.[45]

Limitations

A limitation of this study was the difficulty recruiting those with more advanced disease, and our sample may not be representative of the BT population. Similar to many studies in people with high-grade gliomas, neurocognitive disturbance and rapid tumor progression and deterioration in advanced BT bias recruitment toward those in a relatively stable condition, because the consent process and use of patient-reported outcome measures require adequate cognition. Eligibility criteria would have discouraged participation from people with non–English-speaking or culturally and linguistically diverse backgrounds. Also, with further recruitment, more data for the patient-caregiver dyads would have provided more confidence and opportunity to assess risk factors affecting the couple's sleep.

Another limitation is the absence of objective sleep assessments, such as actigraphy, that can provide reliable information about sleep-wake patterns, nocturnal waking, and daytime inactivity. Although this study adopted the 1-week recall period of PSQI for better recall, discrepancies in the information obtained by different sleep measures have challenged the performance of self-reported sleep outcomes in people with insomnia and chronic medical conditions, such as cancer.[46] It is unclear how participants' subjective reports of sleep disturbance would be compared with objective outcomes, and thus it is difficult to distinguish sleep disturbance as a symptom of fatigue or anxiety from actual malfunctioning of neurophysiology of sleep. Assessing excessive drowsiness in people with BT may be useful in further investigating the association between fatigue and sleep disturbance in people likely to experience the daytime somnolence that is more prevalent in advanced or recurrent BT. Circadian biomarkers, such as core body temperature and plasma levels of melatonin,[47] can also be used in further research to objectively assess disruptions in circadian sleep-wake rhythms. Lastly, no

healthy control individuals were recruited with whom to compare the sleep of patient-participants. There is a paucity of literature describing the sleep experience of patients with malignant BT, and evidence is lacking to suggest a particular variable—typically age, sociocultural status, or chronic/neurological diseases, could pose as a confounder for our analysis.

Implications and Future Directions

We have demonstrated sleep disturbance is a highly prevalent symptom in neuro-oncology patients. Further research is highly warranted for developing and implementing optimal screening and management pathways in clinical practice. Clinicians asking a simple screening question (eg, how is your sleep?) in routine care can be important for identifying sleep-related issues in the patient and his or her caregiver and signaling that sleep disturbance is an important issue warranting the clinician's attention. Interventions that target fatigue and sleep disturbance may benefit people with BT, although further research is warranted to understand underlying mechanisms. Current literature is limited to describing the prevalence of fatigue and its association with QoL in BT.[9] For caregivers, routine screening for anxiety and supportive care to reduce anxiety and mental stress should be offered in conjunction with patient care. Paid caregivers may be used early when family caregivers of people with high-grade gliomas have existing health conditions putting them at greater health risk if combined with caring burden.

The primary objective of this study was to explore the patterns of sleep and the prevalence of sleep disturbance. Given that sleep disturbance can be highly fluctuating[48] and associations with variables may also change, a longitudinal assessment of sleep and potential clinical predictors is warranted to advance our understanding of sleep issues in the patients with BTs. We used 2 sleep assessment tools, PSQI and ISI, with robust psychometric properties supporting applicability in clinical populations, including various cancers. Although their reliability and validity have not been documented in BT,[49] easy administration with minimal imposition both on patients and caregivers and consistency in findings have been exemplified in numerous studies in people with BT.[8,50] The use of actigraphy or polysomnography, supplemented with subjective assessments, may be a superior approach for a complete picture of sleep disturbance.[51] Objective measures would also be used to evaluate the psychometric properties of patient-reported outcomes in people with BT specifically. However, there is a lack of agreed-on procedures for data processing and analysis for the vast amount of, often unnecessarily detailed, objective sleep data, which may go beyond the purpose of a study of sleep disturbance in people with BT.[51] In addition, both feasibility and clinical value of the use of polysomnography may be low, given the high cost and physical and psychological burden on patients with terminal cancer. Interventions for aspects of sleep disturbance most affecting patients and caregivers (eg, subjective perception of poor sleep quality) that can be incorporated into routine care may be more important.

Conclusion

This study demonstrates that sleep disturbance, including both insomnia and drowsiness, are highly prevalent in people with malignant BT and their family caregivers. This warrants more attention in neuro-oncology practice. Other distressing symptoms such as depression, anxiety, fatigue, pain, and neurocognitive difficulties were more severe in patients with sleep disturbance. Fatigue and functional status could be clinical indicators to assess and manage sleep disturbance in patients with BT. High levels of anxiety and psychophysical burden, with long hours of care, are also prevalent in caregivers, impairing their sleep patterns and quality in addition to disturbance from the patient's poor sleep. Tumor- and treatment-related factors had a limited impact on sleep disturbance in our sample, though further investigation is needed to understand the common etiology of comorbid symptoms and identify clinically reversible factors for interventions.

Acknowledgments

We thank Dr Megan Berry, Dr Adam Cooper, Dr Annette Tognela, Dr Vanessa Estall, and Dr Andrew Sunderland for assistance with participant recruitment and data entry.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement. None declared.

References

1. American Academy of Sleep Medicine (AASM), ed. *International Classification of Sleep Disorders: Diagnostic and Coding Manual*. 2nd ed. Westchester, IL: AASM; 2005.
2. Armstrong TS, Vera-Bolanos E, Acquaye AA, Gilbert MR, Ladha H, Mendoza T. The symptom burden of primary brain tumors: evidence for a core set of tumor- and treatment-related symptoms. *Neuro Oncol*. 2016;18(2):252–260.
3. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. *J Clin Oncol*. 2001;19(3):895–908.
4. Delgado-Guay M, Yennurajalingam S, Parsons H, Palmer JL, Bruera E. Association between self-reported sleep disturbance and other symptoms in patients with advanced cancer. *J Pain Symptom Manage*. 2011;41(5):819–827.

5. Savard J, Villa J, Ivers H, Simard S, Morin CM. Prevalence, natural course, and risk factors of insomnia comorbid with cancer over a 2-month period. *J Clin Oncol.* 2009;27(31):5233–5239.
6. Phillips KM, Jim HS, Donovan KA, Pinder-Schenck MC, Jacobsen PB. Characteristics and correlates of sleep disturbances in cancer patients. *Support Care Cancer.* 2012;20(2):357–365.
7. Robertson ME, McSherry F, Herndon JE, Peters KB. Insomnia and its associations in patients with recurrent glial neoplasms. *Springerplus.* 2016;5(1):823.
8. Teke F, Bucaktepe P, Kıbrıslı E, Demir M, Aslıhan I, Inal A. Quality of life, psychological burden, and sleep quality in patients with brain metastasis undergoing whole brain radiation therapy. *Clin J Oncol Nurs.* 2016;20(5):AE–A2.
9. Jeon MS, Dhillon HM, Agar MR. Sleep disturbance of adults with a brain tumor and their family caregivers: a systematic review. *Neuro Oncol.* 2017;19(8):1035–1046.
10. Chow E, Fan G, Hadi S, Wong J, Kirou-Mauro A, Filipczak L. Symptom clusters in cancer patients with brain metastases. *Clin Oncol (R Coll Radiol).* 2008;20(1):76–82.
11. Fox SW, Lyon D, Farace E. Symptom clusters in patients with high-grade glioma. *J Nurs Scholarsh.* 2007;39(1):61–67.
12. Kim BR, Chun MH, Han EY, Kim DK. Fatigue assessment and rehabilitation outcomes in patients with brain tumors. *Support Care Cancer.* 2012;20(4):805–812.
13. Armstrong TS, Gilbert MR. Practical strategies for management of fatigue and sleep disorders in people with brain tumors. *Neuro Oncol.* 2012;14(suppl 4):iv65–iv72.
14. Irwin MR. Depression and insomnia in cancer: prevalence, risk factors, and effects on cancer outcomes. *Curr Psychiatry Rep.* 2013; 15(11):404.
15. Cheng JX, Liu BL, Zhang X, et al. Health-related quality of life in glioma patients in China. *BMC Cancer.* 2010;10:305.
16. Bevans M, Sternberg EM. Caregiving burden, stress, and health effects among family caregivers of adult cancer patients. *JAMA.* 2012;307(4):398–403.
17. Stenberg U, Ruland CM, Miaskowski C. Review of the literature on the effects of caring for a patient with cancer. *Psychooncology.* 2010;19(10):1013–1025.
18. Lee KC, Yiin JJ, Lu SH, Chao YF. The burden of caregiving and sleep disturbance among family caregivers of advanced cancer patients. *Cancer Nurs.* 2015;38(4):E10–E18.
19. Pawl JD, Lee SY, Clark PC, Sherwood PR. Sleep loss and its effects on health of family caregivers of individuals with primary malignant brain tumors. *Res Nurs Health.* 2013;36(4):386–399.
20. Wasner M, Paal P, Borasio GD. Psychosocial care for the caregivers of primary malignant brain tumor patients. *J Soc Work End Life Palliat Care.* 2013;9(1):74–95.
21. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28(2):193–213.
22. Beck SL, Schwartz AL, Towsley G, Dudley W, Barsevick A. Psychometric evaluation of the Pittsburgh Sleep Quality Index in cancer patients. *J Pain Symptom Manage.* 2004;27(2):140–148.
23. Broderick JE, Junghaenel DU, Schneider S, Pilosi JJ, Stone AA. Pittsburgh and Epworth Sleep Scale items: accuracy of ratings across different reporting periods. *Behav Sleep Med.* 2013;11(3):173–188.
24. Morin CM. *Insomnia: Psychological Assessment and Management.* New York: The Guilford Press; 1993.
25. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med.* 2001;2(4):297–307.
26. Savard MH, Savard J, Simard S, Ivers H. Empirical validation of the Insomnia Severity Index in cancer patients. *Psychooncology.* 2005;14(6):429–441.
27. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand.* 1983;67(6):361–370.
28. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap.* 1994;23(2):129–138.
29. Aynehchi BB, Obourn C, Sundaram K, Bentsianov BL, Rosenfeld RM. Validation of the Modified Brief Fatigue Inventory in head and neck cancer patients. *Otolaryngol Head Neck Surg.* 2013;148(1): 69–74.
30. Armstrong TS, Mendoza T, Gning I, et al. Validation of the M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT). *J Neurooncol.* 2006;80(1):27–35.
31. Stern AF. The Hospital Anxiety and Depression Scale. *Occup Med (Lond).* 2014;64(5):393–394.
32. Carroll BT, Kathol RG, Noyes R Jr, Wald TG, Clamon GH. Screening for depression and anxiety in cancer-patients using the Hospital Anxiety and Depression Scale. *Gen Hosp Psych.* 1993;15(2):69–74.
33. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res.* 2011;20(10):1727–1736.
34. Weitzner MA, Jacobsen PB, Wagner H Jr, Friedland J, Cox C. The Caregiver Quality of Life Index–Cancer (CQOLC) scale: development and validation of an instrument to measure quality of life of the family caregiver of patients with cancer. *Qual Life Res.* 1999;8(1-2): 55–63.
35. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist.* 1970;10(1):20–30.
36. Bartlett DJ, Marshall NS, Williams A, Grunstein RR. Sleep health New South Wales: chronic sleep restriction and daytime sleepiness. *Intern Med J.* 2008;38(1):24–31.
37. Brown PD, Ballman KV, Rummans TA, et al. Prospective study of quality of life in adults with newly diagnosed high-grade gliomas. *J Neurooncol.* 2006;76(3):283–291.
38. Gapstur R, Gross CR, Ness K. Factors associated with sleep-wake disturbances in child and adult survivors of pediatric brain tumors: a review. *Oncol Nurs Forum.* 2009;36(6):723–731.
39. Ballesteros-Zebadúa P, Chavarria A, Celis MA, Paz C, Franco-Pérez J. Radiation-induced neuroinflammation and radiation somnolence syndrome. *CNS Neurol Disord Drug Targets.* 2012;11(7):937–949.
40. Shuboni-Mulligan D, Dahut M, Young D, Gilbert M, Armstrong T. RDNA-04. Circadian rhythms and radiation chronotherapy in glioblastoma cell lines and central nervous system cell controls. *Neuro-Oncology.* 2019;21(suppl 6):vi207.
41. Armstrong TS, Ying Y, Wu J, et al. The relationship between corticosteroids and symptoms in patients with primary brain tumors: utility of the Dexamethasone Symptom Questionnaire–Chronic. *Neuro Oncol.* 2015;17(8):1114–1120.
42. Koekkoek JA, Dirven L, Sizoo EM, et al. Symptoms and medication management in the end of life phase of high-grade glioma patients. *J Neurooncol.* 2014;120(3):589–595.
43. Gibbins J, McCoubrie R, Kendrick AH, Senior-Smith G, Davies AN, Hanks GW. Sleep-wake disturbances in patients with advanced cancer and their family carers. *J Pain Symptom Manage.* 2009;38(6): 860–870.
44. Carter PA. A brief behavioral sleep intervention for family caregivers of persons with cancer. *Cancer Nurs.* 2006;29(2):95–103.
45. Rohleder N, Marin TJ, Ma R, Miller GE. Biologic cost of caring for a cancer patient: dysregulation of pro- and anti-inflammatory signaling pathways. *J Clin Oncol.* 2009;27(18):2909–2915.

46. Moore CM, Schmiege SJ, Matthews EE. Actigraphy and sleep diary measurements in breast cancer survivors: discrepancy in selected sleep parameters. *Behav Sleep Med.* 2014:1–19.
47. Dijk DJ, Lazar AS. The regulation of human sleep and wakefulness: sleep homeostasis and circadian rhythmicity. In: Morin CM, Espie CA, eds. *The Oxford Handbook of Sleep and Sleep Disorders.* Oxford: Oxford University Press; 2012.
48. Jeon MS, Dhillon HM, Descallar J, et al. Prevalence and severity of sleep difficulty in patients with a CNS cancer receiving palliative care in Australia. *Neurooncol Pract.* 2019;6(6):499–507.
49. Armstrong TS, Shade MY, Breton G, et al. Sleep-wake disturbance in patients with brain tumors. *Neuro Oncol.* 2017;19(3):323–335.
50. Milbury K, Mallaiah S, Mahajan A, et al. Yoga program for high-grade glioma patients undergoing radiotherapy and their family caregivers. *Integr Cancer Ther.* 2018;17(2):332–336.
51. Madsen MT, Huang C, Gögenur I. Actigraphy for measurements of sleep in relation to oncological treatment of patients with cancer: a systematic review. *Sleep Med Rev.* 2015;20:73–83.