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Sleep Disruption Among Cancer Patients Following Autologous Hematopoietic Cell Transplantation

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Abstract

Despite a high prevalence of sleep disruption among hematopoietic cell transplant (HCT) recipients, relatively little research has investigated its relationships with modifiable cognitive or behavioral factors or used actigraphy to characterize sleep disruption in this population. Autologous HCT recipients who were 6 to 18 months post-transplant completed self-report measures of cancer-related distress, fear of cancer recurrence, dysfunctional sleep cognitions, and inhibitory sleep behaviors upon enrollment. Patients then wore an actigraph for seven days and completed a self-report measure of sleep disruption on day seven of the study. Among the 84 participants (age *M*=60, 45% female), 41% reported clinically-relevant sleep disruption. Examination of actigraph data confirmed that, on average, sleep was disrupted (wake after sleep onset *M*=66 minutes) and sleep efficiency was less than recommended (sleep efficiency *M*=78%). Cancer-related distress, fear of recurrence, dysfunctional sleep cognitions, and inhibitory sleep behaviors were related to self-reported sleep disruption (p's < .05) but not objective sleep indices. Results suggest that many HCT recipients experience sleep disruption after transplant. Cancer-related distress, fear of recurrence, dysfunctional sleep cognitions, and maladaptive sleep behaviors are related to self-reported sleep disruption and should be considered targets for cognitive behavioral intervention in this population.

Keywords

sleep; actigraphy; distress; neoplasm; hematopoietic cell transplant

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Introduction

Sleep disruption is one of the most common quality of life concerns following hematopoietic cell transplantation (HCT),[1,2] with as many as 77% of patients reporting sleep difficulties.[3] Sleep disruption encompasses a variety of sleep complaints including insomnia, which is characterized by problems falling or staying asleep, waking earlier than planned, and/or experiencing non-restorative sleep.[4] Faulhaber and colleagues found that 23% of HCT recipients between 1 and 10 years post-transplant reported problems with insomnia.[5] Moreover, it has been consistently demonstrated that sleep quality is worse among HCT recipients in the post-transplant period compared to healthy individuals.[6–13]

Most evidence regarding sleep disruption among HCT recipients comes from single-item measures incorporated into quality of life questionnaires. These studies may fail to capture the complexity of sleep issues. Additional methodological limitations include small sample sizes and assessment of sleep disruption utilizing mixed samples of autologous and allogeneic transplant recipients. Autologous transplant recipients may experience different rates of sleep disruption than allogeneic recipients, who often receive steroids to treat GVHD, which may interfere with sleep. [26,27] Existing literature is also characterized by exclusive reliance upon self-reports to measure sleep problems with no use of currently available actigraph technology. Actigraphy, which involves the objective measurement of movement by means of an accelerometer[14] has been successfully used to measure sleep/wake patterns in cancer patients[15–19] and correlates at a rate of about 90% agreement with polysomnography.[20] Use of actigraphy is important to provide a more complete picture of sleep disruption among HCT patients.

Given the burden of sleep disruption among HCT patients, it is important to understand risk factors. Prior studies have often generally focused on demographic and clinical predictors.[21] For example, older age[22,23] and female sex[13,24,25] have been reported to be associated with worse sleep quality among HCT recipients. However, data are lacking regarding potentially modifiable risk factors. Cancer-related distress and fear of cancer recurrence have been associated with sleep disruption in breast cancer patients.[28,29] In addition, evidence suggests that dysfunctional sleep-related thoughts and behaviors contribute to the perpetuation of insomnia symptoms in cancer patients and individuals without cancer.[30–33] However, relationships between cognitive-behavioral factors and sleep disruption have not been investigated among HCT recipients.

The goals of the current study were to characterize the prevalence and severity of sleep disruption following autologous HCT measured subjectively and objectively as well as to examine the contribution of modifiable risk factors (i.e., cancer-related distress, fear of cancer recurrence, and dysfunctional sleep related thoughts and behaviors).

Materials and Methods

Participants

Participants were recruited from the Moffitt Cancer Center. Eligible participants: 1) were diagnosed with a hematologic malignancy, 2) were treated with autologous HCT 6 – 18

months prior to study enrollment, 3) were ≥18 years of age, 4) had no history of other cancers other than non-melanoma skin cancer, 5) had no evidence of disease progression at the time of study enrollment, 6) were able to speak and read English, and 7) were able to provide informed consent. The 6 to 18 month timeframe was chosen based on previous literature suggesting sleep quality remains relatively stable following day 100 post-transplant[44,45]. Data were collected from May 2015 to February 2016.

Procedures

The study was approved by the University of South Florida Institutional Review Board. Eligibility was determined via medical record review in consultation with physicians and clinical staff. Patients were recruited during a scheduled outpatient appointment during which they completed an initial questionnaire assessing demographics, cancer-specific factors, and cognitive and behavioral factors related to sleep disruption. They then wore the actigraph for seven consecutive 24-hour periods and completed a sleep log used to aid in determination of bed and rise times. At the end of the monitoring period, participants completed a self-report measure of sleep keyed to the previous seven days.

Measures

Demographic and Clinical Characteristics: Participants completed a standardized self-report form assessing age, sex, race, ethnicity, education, income, marital status, and employment status, a self-report version of the Eastern Cooperative Oncology Group (ECOG) performance status scale, and provided information on recent use of medications to promote sleep. Relevant clinical information (i.e., diagnosis, time since transplant) was collected via medical record review.

Cancer-related Distress: The intrusion subscale of the Impact of Events Scale (IES)[34] is a 7-item self-report measure assessing psychological distress during the past week. The measure was keyed to “cancer and its treatment.” Higher scores indicate greater distress.

Fear of Cancer Recurrence: The Fear of Cancer Recurrence Inventory (FCRI) is a 42-item self-report measure assessing fear or worry that cancer will return or progress.[35] Higher scores indicate greater fear of recurrence.

Dysfunctional Beliefs and Attitudes About Sleep: The Dysfunctional Beliefs and Attitudes about Sleep scale (DBAS-16) is a 16-item, self-report measure assessing faulty beliefs, worries, and attentional biases surrounding sleep-related cognitions (e.g., After a poor night’s sleep, I know it will interfere with my activities the next day).[36] Higher scores indicate more dysfunctional beliefs and attitudes about sleep.

Sleep Effort: The Glasgow Sleep Effort Scale (GSES) is a 7-item self-report measure assessing the extent to which individuals engage in effortful attempts to sleep (e.g., I put too much effort into sleeping when it should come naturally).[37] Higher scores indicate greater sleep effort.

Sleep Hygiene: The Sleep Hygiene Index (SHI) is a 13-item self-report measure assessing the extent to which individuals practice healthy behaviors that facilitate sleep and avoid behaviors that interfere with sleep (e.g., I go to bed at different times from day to day).[38] Higher scores indicate worse sleep hygiene.

Self-reported Sleep Disruption: The Insomnia Severity Index (ISI) is a 7-item self-report measure assessing the nature, severity, and impact of insomnia during the past week.[39] Higher scores indicate worse insomnia symptoms. Total ISI scores are interpreted as follows: 0–7 indicates no clinically significant insomnia, 8–14 indicates subthreshold insomnia, 15–21 indicates clinical insomnia (moderate severity), and 22–28 indicates clinical insomnia (severe).[39]

Objective Sleep Disruption: The Philips Respironics Actiwatch-Score (Philips Healthcare, Andover, MA) was used to objectively quantify sleep patterns. Participants were asked to wear the actigraph on their non-dominant wrist continuously for a seven-day period. Consistent with published recommendations[41], sleep variables examined included sleep efficiency (i.e., percentage of time spent sleeping in relation to time spent in bed), sleep onset latency (SOL, i.e., amount of time taken to fall asleep), wake after sleep onset (WASO, i.e., minutes awake after an extended period of sleep), and total sleep time (TST, i.e., time spent asleep at night). Sleep efficiency served as the primary objective outcome of interest. We used sleep efficiency categories from the Pittsburgh Sleep Quality Index[42] to categorize sleep efficiency in this population.

Statistical Analyses—Data were first examined for normality of distribution and outliers. Mean imputation was used to address sporadic missing items. Multiple imputation was used for scales for which all items were missing (SAS Institute Inc, 2011);[43] the number of imputed data points never exceeded three participants per scale. Descriptive statistics were used to characterize the prevalence and severity of sleep disruption and the sleep indices that could be derived. Pearson correlation coefficients were used to examine relationships between sleep outcomes and demographic and clinical factors and the hypothesized cancer-specific, cognitive, and behavioral risk factors.

Finally, a series of multivariable regression models were conducted to explore the variance in sleep disruption accounted for by demographic and clinical factors, cancer-specific factors, and cognitive and behavioral factors. Demographic and clinical factors significantly correlated with the outcome variables were entered into the first of these models. Cancer-specific factors were then added to the second models. Finally, cognitive and behavioral factors were added to the final models. Data analyses were performed using SAS Version 9.4 (Cary, NC). A p value $< .05$ (two-tailed) was considered statistically significant.

Results

Recruitment and Patient Characteristics

Supplemental Figure 1 depicts participant flow. Demographic and clinical characteristics of the sample (n=84) are shown in Table 1. Patients were an average of 60 years of age. The majority were male (55%), non-Hispanic (94%), white (87%), had completed some college

(64%), and were diagnosed with multiple myeloma (69%). At the time of participation, patients were an average of 350 days post-transplant and the majority reported they were not currently taking sleeping medication (61%).

Prevalence and Severity of Sleep Disruption and Hypothesized Risk Factors

The mean ISI score was 7.07 (SD=5.58); 41% of the sample reported clinically-significant sleep disruption (ISI total scores ≥ 8), with 30% meeting subthreshold insomnia, 10% moderate severity, and 1% severe insomnia. Actigraphy data indicated that, on average, patients took 20 minutes to fall asleep at night, spent approximately one hour awake after initially falling asleep, and spent 6.5 hours asleep. Overall, patients had a mean sleep efficiency of 78%, with 21% meeting sleep efficiency ratings of ≥85%, 50% in the 75 to 84% range, 19% in the 65 to 74% range, and 10% <65%. HCT recipients' subjective reports of sleep disruption were associated with objectively calculated total sleep time, $p = .04$; however, subjectively reported sleep was not associated with any of the other objective measure of sleep disruption, all p's > .05.

On average, patients reported relatively low levels of intrusion ($M = 10.53$, $SD = 8.21$) and functional impairment from fear of cancer progression ($M = 5.82$, $SD = 6.28$) and moderate fear of cancer progression ($M = 15.67$, $SD = 8.04$). The average patient endorsed some dysfunctional beliefs and attitudes about sleep ($M = 3.87$, $SD = 2.07$) as well as sleep effort ($M = 3.52$, $SD = 2.86$) and relatively low levels of unhealthy sleep habits ($M = 26.44$, $SD = 5.39$).

Risk Factors for Sleep Disruption

As shown in Table 2, subjective sleep disruption was not significantly associated with any demographic and clinical variables (p values > .05). Objective sleep disruption was significantly associated with age, ethnicity, and time since transplant. Specifically, younger patients and Hispanic patients demonstrated longer sleep onset latency (p values < .05). Hispanic patients also demonstrated worse sleep efficiency compared to non-Hispanic patients ($p = .05$). In addition, patients who had been transplanted more recently demonstrated shorter total sleep time ($p < .05$).

Relationships of cancer-specific risk factors with subjective and objective sleep disruption appear in Table 2. Intrusive psychological distress as measured by the IES and severity and functional impairment related to fear of cancer progression as measured by the FCRI were related to subjective sleep disruption (p values < .05). Functional impairments resulting from fear of cancer recurrence was related to longer sleep onset latency ($p = .02$). None of the other cancer-specific risk factors were significantly related with any of the objective indices of sleep disruption (p values > .05).

Relationships of cognitive and behavioral risk factors with subjective and objective sleep disruption appear in Table 2. Dysfunctional beliefs and attitudes about sleep as measured by the DBAS, sleep effort as measured by the GSES, and sleep hygiene as measured by the SHI were related to subjective sleep disruption (p values < .05). None of the cognitive and behavioral risk factors were related with any of the objective indices of sleep disruption (p values > .05).

Multivariable Models with Risk Factors for Subjective Sleep Disruption

Table 3 shows results from the multivariable models with subjective sleep disruption as the outcome. No sociodemographic and clinical factors were related to subjective sleep disruption, therefore none were included. The block of variables including IES intrusion, FCRI severity, and FCRI functional impairment scores accounted for 8% of the variance in subjective sleep, with FCRI impairment being the only statistically significant predictor. Patients reporting greater functional impairment also reported worse subjective sleep disruption. When DBAS, GSES, and SHI were added to the model, all factors together accounted for 37% of the variance in subjective sleep ($\Delta R^2 = 29\%$, $F(6, 74) = 5.68$, $p < .001$), with GSES being the only statistically significant predictor. Patients reporting greater sleep effort reported worse subjective sleep disruption.

Multivariable Models with Risk Factors for Objective Sleep Disruption

Table 4 shows results from the multivariable models with objective sleep disruption as the outcome. In the first model, age and ethnicity were entered and accounted for 12% of the variance in sleep onset latency, with younger patients and Hispanic patients taking longer to fall asleep. In the second model, IES intrusion, FCRI severity, and FCRI functional impairment were added and accounted for an additional 9% of the variance in sleep onset latency; however, none of the added factors were statistically significant. In the final combined model, DBAS, GSES, and SHI were entered in addition to the other factors. All factors entered together accounted for 23% of variance in sleep onset latency, but ethnicity remained as the only statistically significant predictor.

Discussion

The present study characterized sleep disruption measured subjectively and objectively and examined potential demographic, clinical, cancer-specific, cognitive, and behavioral risk factors for sleep disruption among autologous HCT recipients between 6 and 18 months post-transplant. A total of 41% of patients reported clinically relevant sleep disruption. While estimates of the prevalence of sleep disruption in HCT patients vary widely, results from the present study are generally in line with estimates in the survivorship period following HCT.[5,22,26,44,45] Actigraphy revealed that patients spent over an hour awake after falling asleep and spent an average of 6.5 hours asleep at night. Patients took approximately 20 minutes to fall asleep at night and average sleep efficiency was 78%, which is below the recommended 85% often used as a cut point to indicate healthy sleep.[46] Taken together, these descriptive data indicate that a large proportion of autologous HCT patients experience poor sleep.

In univariate analyses, cancer-specific, cognitive, and behavioral factors were associated with subjective but not objective sleep disruption. In multivariable models, only sleep effort as measured by the GSES emerged as a significant predictor of subjective sleep disruption. This pattern of results indicates that it may be patients' distorted cognitions, more than cancer-related distress or unhealthy sleep habits that are the primary drivers of their self-reported sleep disruption. If this is the case, it may be particularly important to change distorted cognitions in addressing HCT patients' sleep complaints. In multivariable models

with objectively measured sleep onset latency as the outcome, demographic factors demonstrated the strongest relationship, with Hispanic ethnicity emerging as the only significant predictor of worse sleep onset latency. Randomized controlled trials of psychologically-based sleep interventions with cancer patients have generally demonstrated a reduction in objectively measured sleep disruption following intervention delivery.[46–48] However, these studies mostly recruited patients with breast cancer and therefore may not generalize to the autologous HCT setting.

The lack of relationship found between subjectively and objectively measured sleep is consistent with previous research and suggests that these two methods of sleep measurement assess different aspects of sleep. The finding that self-reported cognitive and behavioral factors were not associated with objective sleep in the present study raises the question of whether sleep interventions that target these mechanisms (e.g., CBT-I, MBSR) improve objective indices of sleep among autologous transplant recipients or may improve objective sleep through other mechanisms not assessed in this study (e.g., self-efficacy for managing sleep disturbance). Nevertheless, cancer-specific, cognitive, and behavioral factors were related to subjective reports of sleep, which is the more clinically-relevant outcome. No studies have been conducted of CBT-I or MBSR for sleep in HCT recipients. Because CBT-I and MBSR are evidenced-based treatments to improve sleep and, unlike medication, do not have the potential for side effects or dependency, they should still be considered for autologous HCT patients who report significant sleep disturbance.

Study limitations include the cross-sectional assessment of sleep, which prevented examination of how relationships between cancer-related, cognitive, and behavioral factors and sleep disruption change over time. Future research should examine changes in objective sleep longitudinally. The study was also limited by the lack of ethnic and racial diversity of its participants, which limits generalizability to other groups. In addition, the majority of the sample was diagnosed with multiple myeloma. Because autologous transplant is not curative for this disease cancer-related distress may be higher in these patients than in those with other diagnoses. Finally, other potential contributing factors (e.g., pain) were not assessed. Despite these limitations, the present study adds to a strong foundation of prior literature examining perpetuating factors of insomnia. Moreover, this study investigated not only subjective but also objective sleep disruption among a homogenous group of autologous transplant recipients, which to the best of our knowledge has not been done in HCT recipient survivorship.

In summary, patients reporting subjective sleep disruption should be referred for pharmacological or psychological sleep intervention after ruling out other concomitant medical conditions. Results from the present study suggest that a large proportion of autologous HCT recipients have dysfunctional cognitions about sleep and maladaptive sleep habits, both of which are targets for sleep interventions such as CBT-I. Moreover, CBT-I is a recommended treatment for clinical sleep issues in cancer patients.[30,46,47] MBSR is another treatment with demonstrated efficacy among cancer patients.[49,50] Future research should investigate the efficacy of interventions such as CBT-I and MBSR with autologous HCT recipients, particularly for those patients who report moderate to severe sleep disruption.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and Medical Characteristics (N = 84)

Characteristic	
Age, years	
M	59.67
SD	11.91
Gender, No. (%)	
Male	46 (54.8)
Female	38 (45.2)
Ethnicity, No. (%)	
Not Hispanic	79 (94.0)
Hispanic	4 (4.8)
Missing	1 (1.2)
Race, No. (%)	
White	73 (86.9)
Nonwhite	11 (13.1)
Marital Status, No. (%)	
Married	64 (76.2)
Not married	20 (23.8)
Education, No. (%)	
High school or less	26 (31.0)
College or more	34(67.8)
Missing	1 (1.2)
Employment, No. (%)	
Work full-time or part-time	26 (31.0)
Retired	32 (38.1)
Other	25 (29.7)
Missing	1 (1.2)
Income, No. (%)	
< 40K	31 (36.9)
≥ 40K	36 (42.9)
Prefer Not To Answer/Missing	17 (20.2)
Cancer type, No. (%)	
Multiple Myeloma	58 (69.0)
Hodgkin lymphoma	8 (9.5)
Non-Hodgkin lymphoma	16 (19.1)
Amyloidosis	2 (2.4)
Time since transplant, days	
M	349.98
SD	123.89
Functional Status, No. (%)	
4	40 (47.6)

Characteristic	
3	35 (41.7)
2	6 (7.1)
1	1 (1.2)
Missing	2 (2.4)
Sleeping Medication, No. (%)	
Yes	32 (38.1)
No	51 (60.7)
Missing	1 (1.2)

Note. SD = standard deviation.

Table 2

Relationships Between Demographic and Clinical Risk Factors, Cancer-Specific Risk Factors, Cognitive and Behavioral Risk Factors, and Subjective and Objective Sleep Disturbance

	ISI total score	SE	SOL	WASO	TST
Demographic and Clinical Risk Factors					
Gender	0.11	0.07	0.03	−0.11	0.07
Ethnicity	0.15	**0.22** *	**−0.30** **	−0.05	0.10
Married	−0.03	−0.02	0.13	−0.06	0.05
Education	0.01	0.08	−0.01	0.03	0.03
Age	−0.10	0.17	**−0.25** *	−0.06	0.14
Diagnosis	0.09	0.16	−0.18	−0.09	0.03
Time since transplant	−0.12	0.17	−0.10	−0.04	**0.24** *
Cancer-Specific Risk Factors					
IES Intrusion	**0.25** *	0.17	−0.02	−0.09	0.14
FCRI Severity	**0.25** *	0.09	0.13	−0.04	0.17
FCRI Impairment	**0.32** **	−0.18	**0.23** *	0.11	−0.06
Cognitive and Behavioral Risk Factors					
DBAS	**0.54** ***	−0.01	0.18	0.02	0.08
GSES	**0.67** ***	−0.13	0.21	0.07	−0.06
SHI	**0.28** *	−0.04	0.07	−0.08	−0.17

Note. Table depicts r coefficients. Significant coefficients are bolded and marked with asterisks,

* p < .05,

** p < .01,

*** p < .001. Categorical variables were dichotomized and run as correlations.

ISI = Insomnia Severity Index, SE = Sleep Efficiency, SOL = Sleep Onset Latency, WASO = Wake After Sleep Onset, TST = Total Sleep Time, IES = Impact of Events Scale, FCRI = Fear of Cancer Recurrence Inventory, DBAS = Dysfunctional Beliefs and Attitudes about Sleep, GSES = Glasgow Sleep Effort Scale, SHI = Sleep Habits Index.

Table 3

Multivariable Hierarchical Regression Models with Subjective Sleep Disruption

Risk Factors	R^2	β	*p*
Cancer-Specific Risk Factors	0.08	-	-
IES Intrusion	-	0.12	.36
FCRI Severity	-	0.05	.74
FCRI Impairment	-	0.25	.05
With Cognitive and Behavioral Factors	0.37	-	-
IES Intrusion	-	0.05	.61
FCRI Severity	-	−0.16	.18
FCRI Impairment	-	0.10	.29
DBAS	-	0.18	.11
GSES	-	0.55	< .001
SHI	-	0.04	.69

Note: IES = Impact of Events Scale, FCRI = Fear of Cancer Recurrence Inventory, DBAS = Dysfunctional Beliefs and Attitudes about Sleep, GSES = Glasgow Sleep Effort Scale, SHI = Sleep Habits Index.

Table 4

Multivariable Hierarchical Regression Models with Sleep Onset Latency

Risk Factors	R^2	β	*p*
Demographic & Clinical Risk Factors	0.12	-	-
Age	-	−0.22	.04
Ethnicity	-	−0.27	.01
With Cancer-Specific Risk Factors	0.21	-	-
Age	-	−0.20	.05
Ethnicity	-	−0.26	.01
IES Intrusion	-	−0.20	.12
FCRI Severity	-	0.16	.26
FCRI Impairment	-	0.17	.16
With Cognitive and Behavioral Factors	0.23	-	-
Age	-	−0.20	.07
Ethnicity	-	−0.28	.008
IES Intrusion	-	−0.21	.10
FCRI Severity	-	0.11	.46
FCRI Impairment	-	0.14	.28
DBAS	-	0.08	.56
GSES	-	0.13	.41
SHI	-	−0.06	.62

Note: SOL = Sleep Onset Latency, IES = Impact of Events Scale, FCRI = Fear of Cancer Recurrence Inventory, DBAS = Dysfunctional Beliefs and Attitudes about Sleep, GSES = Glasgow Sleep Effort Scale, SHI = Sleep Habits Index.