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Cognitive Problems Following Hematopoietic Stem Cell Transplant: Relationships with Sleep, Depression, and Fatigue

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Abstract

Cognitive problems are a significant, persistent concern for patients undergoing hematopoietic stem cell transplant (HSCT). Sleep is important for many cognitive tasks; however, the relationship between sleep and cognitive problems for HSCT patients is unknown. This study examined the relationship between sleep and cognitive problems for HSCT patients from pre to post-transplant. Patients undergoing HSCT (N=138) completed questionnaires at pre-transplant and during the 12 months following transplant. Questionnaires assessed sleep and cognitive problems as well as commonly co-occurring symptoms: depressive symptoms, fatigue, and pain. Post-hoc analyses examined the relationship of specific sleep problems with cognitive problems. Sleep problems covaried with cognitive problems even after controlling for depressive symptoms, fatigue, and pain. Depressive symptoms and fatigue were also uniquely related to cognitive problems. Post-hoc analyses suggest that sleep somnolence, shortness of breath, snoring, and perceptions of inadequate sleep may contribute to the association found between sleep and cognitive problems. Findings suggest that sleep problems are associated with and may contribute to cognitive problems for HSCT patients. However, sleep problems are rarely screened for or discussed during clinic visits. Assessing and treating specific sleep problems in addition to depressive symptoms and fatigue may have implications for improving cognitive problems for HSCT patients.

Cognitive problems are a significant, though understudied, concern for patients undergoing hematopoietic stem cell transplant (HSCT). More than 50% of HSCT patients report cognitive problems, with over 25% indicating these problems are moderate to severe[1, 2]. Cognitive problems following HSCT have been identified in the domains of memory,

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attention and concentration, executive functioning, mental processing speed, visual memory, and motor function[2-4]. These problems are an important quality of life concern for HSCT patients. Patients who report cognitive problems are also likely to report difficulties with emotional, physical, and social functioning[2, 3, 5, 6] as well as less confidence in their abilities to manage HSCT-related symptoms[6].

Sleep is important for many cognitive tasks, including attention and executive functioning, memory consolidation, and procedural and visuospatial learning; poor sleep quality is associated with reduced general cognitive functioning[7-13]. While research from the general population[14] and patients with chronic illnesses (e.g., heart failure[15], Parkinson's disease[11]) has identified a relationship between sleep and cognitive problems, limited work has examined this relationship among cancer patients. What is known comes from cross-sectional studies and suggests that sleep problems are associated with patients' self-reported memory[16] and cognitive problems[17, 18]. In one recent study, cancer survivors with sleep disordered symptoms (i.e., snoring, frequent gasping during sleep) were nine times more likely to report memory problems[16]. Similarly, breast cancer survivors reporting poorer sleep quality experience worse perceptions of their cognitive functioning and greater cognitive impairments[17].

The factors that contribute to cognitive problems following HSCT are not well understood yet poor sleep quality is a significant concern that often begins prior to transplant or during hospitalization[19-23]. In a recent study, more than half of HSCT patients experienced poor sleep quality, with sleep disturbance and sleep onset latency among the most commonly reported problems[24]. Recent research has found the use of sleep medications by HSCT patients to significantly increase during hospitalization; in one study, 8% of those surveyed were using sleep medications prior to hospitalization, while more than half (65.9%) used sleep medications during hospitalization[23]. Other research suggests that sleep problems may peak one-month following transplant and continue for as long as a year after patients return home[21, 24].

Patients' sleep difficulties may be associated with a variety of factors including, medications provided as part of their pre- and post-transplant treatment regimens. For example, pre- and post-transplant treatment regimens often include high dose corticosteroids (e.g., dexamethasone[25]), which have been linked to reductions in REM sleep, increased REM latency, and difficulties staying asleep.[26, 27] A better understanding of the connection between sleep and cognitive problems is needed in patients undergoing HSCT and could provide important information for improving the management of these symptoms.

The present study had two aims. First, we examined change from pre- to post-transplant for both sleep and cognitive problems. Second, we examined the relationship between sleep and cognitive problems. Because depressive symptoms, fatigue, and pain co-occur with sleep problems among cancer patients[28-36], we also examined change in these variables from pre- to post-transplant. Analyses examining the relationship between sleep and cognitive problems included these important co-occurring symptoms. Post-hoc analyses examined the relationships between specific dimensions of sleep problems (e.g., sleep disturbance, snoring, and somnolence) and cognitive problems.

Method

Participants and Procedure

Patients undergoing autologous or allogeneic HSCT were recruited from a bone marrow transplant clinic between August 2011 and January 2014. Patients completed an assessment pre-transplant and at least one assessment in the three to twelve months post-transplant. Patients completed questionnaires about their symptoms, daily functioning, and quality of life. Given the health status of many HSCT patients, questionnaires were administered in short-format, and subscales were selected from larger questionnaires to reduce overall burden. Exclusion criteria included inability to complete self-report questionnaires due to language or medically documented severe cognitive impairment (e.g., Alzheimer's Disease, Dementia) and receipt of hospice care. Patients who were diagnosed with chronic, severe graft versus host disease (GVHD),[37] as indicated by documentation in their medical record, were excluded from the present analyses.

Pre-transplant questionnaires were completed in clinic and returned to clinic staff. Four hundred twenty-seven patients were identified pre-transplant: 61.1% (n=261) completed a pre-transplant assessment, 21.8% (n=93) had begun their preparative regimen or were too ill to complete pre-transplant questionnaires but participated in the study post-transplant, and 17.1% (n=73) declined participation. Post-transplant assessments were completed by mail or web-based platform (Qualtrics) after patients returned home. Patients completed at least one questionnaire at 3, 6, and/or 12 months post-transplantation. This study was approved by the university Institutional Review Board. All participants completed informed consent.

Data from patients completing questionnaires at both pre- and post-transplant were included in the analyses. Of the 261 patients who completed pre-transplant questionnaires, 52.9% (n=138) completed assessments post-transplant, 6.5% were excluded due to a diagnosis of post-transplant chronic, severe graft versus host disease (GVHD; n=17), 15.7% (n=41) were deceased, and 24.9% (n=65) did not return any post-transplant questionnaires. When compared on sociodemographic variables, groups did not differ for race (p=.94) or gender (p=.20); however, groups differed on age, with GVHD patients and those who did not return a post-transplant assessment being on average 12 and 5 years younger than those with both pre- and post-transplant assessments, respectively (p<.001). When compared on pre-transplant variables of interest, there were no significant differences for depressive symptoms, pain, fatigue, or cognitive problems. Groups differed for sleep problems (p=.02), with deceased participants experiencing fewer pre-transplant sleep problems.

Of the 138 participants with pre- and post-transplant assessments, 57% (n=78) completed more than one post-transplant assessment (3-months: n=94;6-months: n=87; 12-months:n=61).

Measures

Cognitive problems—The 8-item PROMIS Applied Cognitive-General Concerns Scale[38] measured cognitive problems. Patients rated the degree and impact of cognitive difficulties over the past seven days including mental acuity, concentration, memory, verbal fluency, multi-tasking, interference, and functional change[39]. A 5-point response scale ranging from

1 (never) to 5 (very often/several times a day) was used. Items were summed, and possible scores ranged from 5-40. Higher scores represent greater cognitive problems. This scale is reliable and valid when used with chronic illness populations[40]. Cronbach's alpha in this sample ranged from 0.96-0.97 across assessments.

Sleep problems—The Medical Outcomes Study (MOS) Sleep Scale[41, 42] is a 12-item measure developed for patients with chronic illness. The measure is divided into six dimensions evaluating sleep disturbance, snoring, shortness of breath, perceived adequacy, somnolence, and quantity. Patients rate each item over the last 4 weeks. The sleep problems index is derived by creating a composite score for the six dimensions which is transformed to a 0-100 scale; higher scores reflect more sleep problems. This scale is widely used with patients with cancer[43] and is reliable and valid[44-46]. Cronbach's alpha was 0.78-0.85.

Depressive Symptoms—The PROMIS 6-item depression scale[47] assessed negative mood (sadness, guilt), views of self (self-criticism, worthlessness), social cognition (loneliness, interpersonal alienation), and decreased positive affect and engagement (loss of interest, meaning, and purpose). Items were answered on a 5-point scale ranging from 1 (never) to 5 (always). Items were summed and converted to standardized T-scores; higher T-scores represent more depressive symptoms[48]. Cronbach's alpha was 0.92-0.94.

Fatigue—The PROMIS 6-item fatigue scale[47] assessed a range of fatigue symptoms, from mild, subjective feelings of tiredness to a sustained sense of exhaustion. This scale measured the experience (i.e., frequency, duration, and intensity) and impact of fatigue. Items were rated on a 5-point scale ranging from 1 (not at all) to 5 (very much), summed, and then converted to standardized T-scores; higher T-scores represent greater fatigue. The PROMIS fatigue scale has good reliability and validity when used with the general population[47] and those with chronic illnesses[49, 50]. Cronbach's alpha was 0.95-0.96.

Pain—The Brief Pain Inventory (BPI)[51] intensity scale assessed pain severity. This measure contains four 0-10 scale ratings corresponding to the patient's pain intensity over the past week. A composite score was created by averaging these items, with higher scores indicating greater pain intensity. Prior studies have shown the measure to have good internal reliability, test-retest reliability, and validity[52]. Cronbach's alpha was 0.85-0.92.

Statistical Analysis

Longitudinal Analyses—Longitudinal linear mixed models were conducted using SPSS v.19[53] to examine changes in sleep, cognitive problems, depression, and fatigue from pre- to post-transplant. Transplant type was included as a covariate in each model given the differences in preparative regimens among patients receiving autologous versus allogeneic transplant (e.g., myeloablative vs. non-myeloablative preparative regimen)[54]. Transplant type was coded as 0=autologous, 1=allogeneic transplant. Time was coded as months since transplant. Statistical significance was considered at the level of $p<0.05$, two-tailed. The data conform to the assumptions of this test.

Multivariate analyses—A multivariate linear mixed model examined the relationship between sleep and cognitive problems using SPSS v.19[53]. This analytic approach uses all available data and allows for randomly missing observations within a participant. Data were nested within participants to address non-independence due to repeated measures and to account for data from participants with more than one post-transplant assessment. The model included sleep, depressive symptoms, fatigue, and pain as time-varying covariates and also controlled for time (coded as months from transplant) as well as age and transplant type, two variables known to be associated with cognitive problems. Post-hoc analyses examined the relationship between specific sleep problems and cognitive problems using multivariate linear mixed models. Statistical significance was considered at the level of $p<0.05$, two-tailed. The data conform to the assumptions of these tests.

Results

Sample Description

Participants (N=138) were primarily male (60.1%) and Caucasian (84.8%) and on average 60.4 years old (see Table 1). Approximately 42.8% completed college and/or graduate work, 30.4% were retired, 26.8% were employed, and 29.0% were on medical disability. The majority of patients received autologous HSCT (76.5%).

Longitudinal Analyses

Longitudinal linear mixed models were run separately with cognitive problems, sleep problems, depression, fatigue, and pain as dependent variables. The models estimated time, transplant type (allogeneic vs. autologous), and time × transplant type. The time effect tested whether the variables changed from pre- to post-transplant and across the post-transplant assessments. Results of the fixed effects are presented in Table 2. There was no significant effect of time for cognitive problems, sleep problems, depressive symptoms, or pain (*ps*>0.05). The magnitudes of the slopes suggest that these variables remained stable over time. The time effect for fatigue bordered on significance (B=-0.21, SE=0.11, t=-2.08, p=0.06), suggesting that fatigue decreased over time in this sample. Transplant type was significantly associated with pain and fatigue, with patients who received autologous transplants reporting greater pre-transplant pain (B=-3.23, SE=1.55, t=-2.08, $p<0.04$) and fatigue (B=-0.81, SE=0.39, t=-2.07, p=0.04). The time × transplant type effects were not significant (ps>0.05), indicating that the rate of change in the variables of interest did not differ by transplant type.

Multivariate Analysis

Table 3 reports fixed effects for the multivariate model examining the covariation of sleep and cognitive problems controlling for months since transplant, age, and transplant type. Sleep problems were significantly associated with cognitive problems (B=0.07, p=0.002) after accounting for depressive symptoms, fatigue, and pain. This suggests that sleep problems are associated with cognitive problems above and beyond the effect of these other symptoms. Depressive symptoms (B=0.31, $p<0.01$) and fatigue (B=0.18, $p<0.01$) were also uniquely related to cognitive problems such that patients who experienced more depressive symptoms and/or greater fatigue experienced more cognitive problems. Pain was not associated with cognitive problems.

Post-Hoc Analyses

Post-hoc analyses examined the relationship between specific dimensions of sleep problems (i.e., somnolence, shortness of breath, snoring, sleep adequacy, sleep disturbance, quantity) and cognitive problems after controlling for months since transplant, depressive symptoms, fatigue, pain, age, and transplant type. Separate models were conducted for each sleep problem. Sleep somnolence (B=0.06, SE=0.02, t=3.09, p=0.002), shortness of breath (B=0.04, SE=0.02, t=2.38, p=0.02), snoring (B=0.03, SE=0.01, t=2.42, p=0.02), and sleep adequacy (B=-0.03, SE=0.01, t=-2.04, p=0.04) significantly covaried with cognitive problems. Sleep disturbance and number of hours of sleep were not significantly associated with cognitive problems (p's>0.05). Significant associations remained between depressive symptoms and fatigue and cognitive problems in all models.

Discussion

This study examined the relationship between sleep and cognitive problems in patients who have undergone HSCT. Overall, sleep and cognitive problems remained stable pre- to post -transplant, and the trajectories of change did not differ by transplant type. Mean levels of cognitive problems were similar to those experienced by patients with chronic diseases associated with cognitive decline and impairment (i.e., Multiple Sclerosis)[40]. The sample average for sleep problems was approximately half a standard deviation higher than the mean for the general population,[46] suggesting HSCT patients experience more sleep problems than the general population.

Sleep problems covaried with cognitive problems such that patients with more sleep problems also had more cognitive concerns. The relationship between sleep and cognitive problems was found after controlling for depressive symptoms, fatigue, and pain, symptoms known to cluster with sleep problems among cancer patients[34, 55]. This suggests that sleep problems endorsed by HSCT patients may independently contribute to cognitive problems above and beyond the effect of commonly co-occurring symptoms. Specific dimensions of sleep difficulties including sleep somnolence, shortness of breath, snoring, and sleep adequacy may account for the unique relationship between sleep and cognitive problems. Depressive symptoms and fatigue were also significantly associated with cognitive problems in multivariate and post-hoc models, which is consistent with prior research[56] showing HSCT patients with more depressive symptoms or greater fatigue experience more cognitive problems[1, 57].

The presence of sleep problems can contribute to the diagnosis of depression[58]; however, the relationship between depressive symptoms and cognitive problems occurred independent of the relationship between sleep and cognitive problems. This finding suggests many of the sleep problems associated with cognitive problems among HSCT patients may be distinct from those commonly found among individuals with depressive symptoms. Two domains of sleep difficulties that commonly co-occur with depressive symptoms (i.e., sleep disturbance, numbers of hours slept) were no longer associated with cognitive problems after accounting for depressive symptoms.

Cancer-related fatigue is a common and persistent concern for cancer survivors[59], including HSCT patients[60]. While sleep problems and fatigue are correlated[35, 36, 60], cancer-related fatigue often does not improve following sleep[36] suggesting that fatigue and sleep problems may be distinct symptoms. This study provides support for the distinction between sleep problems and fatigue, as each independently contributed to cognitive problems for HSCT patients.

While sleep problems affect many HSCT patients, a recent survey of 180 HSCT physicians revealed that patients and physicians rarely discussed sleep disruption during clinic visits[61]. Only 17% of physicians reported having discussions about sleep during at least half of patient visits. A first step to addressing sleep problems among HSCT patients is to routinely assess these symptoms. This can be done in a variety of ways including a nurse-led assessment or via electronic assessment prior to clinic appointments. Information obtained from actigraphs[62] or patients' personal activity trackers (e.g., Fitbit) may also provide objective sleep data to guide sleep discussions.

The results of the present study have important clinical implications for treating cognitive problems reported by HSCT patients. Specifically, three types of symptoms should be considered: sleep problems, depressive symptoms, and fatigue. The use of symptom-specific techniques may assist with improving cognitive functioning.

First, specific sleep difficulties (i.e., somnolence, shortness of breath, snoring, sleep adequacy) significantly associated with cognitive problems may occur in the context of sleep apnea syndrome (SAS). SAS is often worsened or complicated by chemotherapy, radiation, and other cancer therapies[63, 64]. There are many possible treatments for SAS, the most prevalent being Continuous Positive Airway Pressure (CPAP) therapy[65]. CPAP therapy may alleviate the respiratory-related sleep problems that likely contribute to cognitive problems for some HSCT patients. A clinical workup of sleep problems (e.g., sleep study) is recommended for patients with suspected SAS.

Second, psychosocial interventions may benefit patients who do not exhibit clear breathing-related sleep problems. Given that sleep disturbances are often related to depressive symptoms and fatigue, managing these symptoms concurrently may be beneficial for also addressing cognitive problems. Cognitive-behavioral therapy for insomnia (CBTi) has been shown to not only improve sleep but also result in generalized improvements in depression and fatigue in cancer patients with insomnia[66-68]. In one study, when compared to usual care, patients receiving CBTi saw a greater reduction in clinically significant insomnia (17.5% reduction vs. 52% reduction), fatigue (2.5% increase vs. 10.9% reduction) and depression (5% increase vs. 5.5% decrease)[66].

Sleep hygiene recommendations (e.g., reducing caffeine intake, keeping consistent sleep/wake times) are an important component of CBTi protocols[69]. A sleep hygiene intervention offered to patients prior to transplantation may assist them with maintaining good sleep during hospitalization and following their return home. Assistance with improving the sleep environment during hospitalization is also important. Aspects of the hospital environment may leave patients vulnerable to sleep problems[70]. Several strategies have been suggested to address barriers to sleep during hospitalization[70] including those that address noise (e.g., offering earplugs), lighting (i.e., offering eye masks), and the effects of treatment (e.g., reducing the frequency of overnight monitoring).

Third, patients may benefit from exercise-based interventions. A recent review[71] found that participating in aerobic exercise (e.g., home-based walking, bed cycle ergometer), resistance training, and mindfulness-based exercise (i.e., yoga) designed for cancer survivors produced improvements in sleep, depressive symptoms, fatigue, and cognitive problems. In one study, HSCT patients who began using a cycle ergometer six days prior to transplant and continued post-transplant saw significant improvements in emotional state while those in the control group saw worsening of fatigue[72]. In another study, HSCT patients randomized to participate in endurance-based exercises and strength training experienced reductions in fatigue and distress over time[73]. Jarden and colleagues[74] found that, when compared to a control group, HSCT patients randomized to a multimodal exercise intervention (i.e., stationary cycling, dynamic and stretching exercises, and resistance training) experienced fewer cognitive symptoms (i.e., diminished concentration, memory problems) at 6-month follow-up.

Sleep and cognitive problems were stable over time, from pre- to post-transplant, suggesting that the contribution of transplant to these variables may be unclear. It appears that for many patients, their prior treatments and pre-transplant preparative regimens may contribute to pre-transplant sleep[21] and cognitive problems.[75] Regardless of the direct impact of transplant on these variables, sleep and cognitive problems continue to be important quality of life concerns for HSCT patients throughout the disease trajectory and are important intervention targets. The interventions (e.g., psychosocial, cognitive-behavioral, exercise-based, etc.) described previously can help to improve quality of life and outcomes for transplant patients, and the results of the present study suggest that early intervention may be beneficial.

In the present study, sleep and cognitive problems were assessed via self-report questionnaires rather than objective measures. The self-report measures used in the present study have been well validated, and self-reported measures of sleep and cognitive problems have been associated with objective measures. For example, self-reported perceptions of cognitive decline have been correlated with underlying neurodegenerative changes even in the absence of measurable cognitive changes on a neuropsychological assessment[76]. Further, self-report measures of sleep may tap into sleep-related phenomena that cannot be assessed via objective measures[77]. Future studies utilizing objective measures of sleep and cognitive problems in addition to self-reported measures with HSCT patients are necessary to confirm the results of the present study.

The present study has several strengths including a longitudinal design, controlling for symptoms (depression, fatigue, pain) that often cluster with sleep problems, post-hoc analyses examining the relationship of specific sleep problems to cognitive problems, and the use of a robust analytic strategy to ensure inclusion of cases with missing data. The study has limitations that merit acknowledgment. First, the relatively small sample size and the fact that the HSCT patients accrued were primarily Caucasian and received autologous transplants due to the nature of their disease (primarily multiple myeloma[78]) may limit the generalizability of the results to other racial/ethnic groups and patient populations. Second, sleep and cognitive problems were assessed concurrently therefore causality cannot be ascertained. Additional longitudinal studies are necessary to determine the direction of the relationship between sleep and cognitive problems. Future studies should also examine whether interventions targeting sleep problems, depressive symptoms, and fatigue result in improvements in cognitive problems among HSCT patients.

In sum, this study suggests that sleep problems, depressive symptoms, and fatigue may independently contribute to cognitive problems experienced by HSCT patients. Knowledge of these three domains underscores the importance of developing targeted screening measures and interventions to address the cognitive concerns of HSCT patients.

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References

1. Booth-Jones M, Jacobsen PB, Ransom S, Soety E. Characteristics and correlates of cognitive functioning following bone marrow transplantation. Bone Marrow Transplant. 2005; 36(8):695–702. e-pub ahead of print 2005/08/09. DOI: 10.1038/sj.bmt.1705108 [PubMed: 16086044]
2. Harder H, Cornelissen JJ, Van Gool AR, Duivenvoorden HJ, Eijkenboom WM, van den Bent MJ. Cognitive functioning and quality of life in long-term adult survivors of bone marrow transplantation. Cancer. 2002; 95(1):183–192. e-pub ahead of print 2002/07/13. DOI: 10.1002/cncr.10627 [PubMed: 12115332]
3. Meyers CA, Weitzner M, Byrne K, Valentine A, Champlin RE, Przepiorka D. Evaluation of the neurobehavioral functioning of patients before, during, and after bone marrow transplantation. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1994; 12(4):820–826. e-pub ahead of print 1994/04/01. [PubMed: 8151324]
4. Syrjala KL, Dikmen S, Langer SL, Roth-Roemer S, Abrams JR. Neuropsychologic changes from before transplantation to 1 year in patients receiving myeloablative allogeneic hematopoietic cell transplant. Blood. 2004; 104(10):3386–3392. e-pub ahead of print 2004/07/15. DOI: 10.1182/blood-2004-03-1155 [PubMed: 15251983]
5. Saleh US, Brockopp DY. Quality of life one year following bone marrow transplantation: psychometric evaluation of the quality of life in bone marrow transplant survivors tool. Oncol Nurs Forum. 2001; 28(9):1457–1464. e-pub ahead of print 2001/10/31. [PubMed: 11683315]
6. Wu LM, Austin J, Hamilton JG, Valdimarsdottir H, Isola L, Rowley S, et al. Self-efficacy beliefs mediate the relationship between subjective cognitive functioning and physical and mental well-being after hematopoietic stem cell transplant. Psycho-oncology. 2012; 21(11):1175–1184. DOI: 10.1002/pon.2012 [PubMed: 21739524]
7. Gais S, Plihal W, Wagner U, Born J. Early sleep triggers memory for early visual discrimination skills. Nature neuroscience. 2000; 3(12):1335–1339. e-pub ahead of print 2000/12/02. DOI: 10.1038/81881 [PubMed: 11100156]
8. Goel N, Rao H, Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. Seminars in neurology. 2009; 29(4):320–339. e-pub ahead of print 2009/09/11. DOI: 10.1055/s-0029-1237117 [PubMed: 19742409]
9. Mednick SC, Makovski T, Cai DJ, Jiang YV. Sleep and rest facilitate implicit memory in a visual search task. Vision research. 2009; 49(21):2557–2565. e-pub ahead of print 2009/04/22. DOI: 10.1016/j.visres.2009.04.011 [PubMed: 19379769]

10. Smith C. Sleep states and memory processes in humans: procedural versus declarative memory systems. Sleep medicine reviews. 2001; 5(6):491–506. e-pub ahead of print 2003/01/18. DOI: 10.1053/smrv.2001.0164 [PubMed: 12531156]
11. Stavitsky K, Neargarder S, Bogdanova Y, McNamara P, Cronin-Golomb A. The impact of sleep quality on cognitive functioning in Parkinson's disease. Journal of the International Neuropsychological Society : JINS. 2012; 18(1):108–117. e-pub ahead of print 2011/12/14. DOI: 10.1017/S1355617711001482 [PubMed: 22152279]
12. Stickgold R. Sleep-dependent memory consolidation. Nature. 2005; 437(7063):1272–1278. e-pub ahead of print 2005/10/28. DOI: 10.1038/nature04286 [PubMed: 16251952]
13. Stickgold R, Hobson JA, Fosse R, Fosse M. Sleep, learning, and dreams: off-line memory reprocessing. Science. 2001; 294(5544):1052–1057. e-pub ahead of print 2001/11/03. DOI: 10.1126/science.1063530 [PubMed: 11691983]
14. Ohayon MM, Vecchierini MF. Normative sleep data, cognitive function and daily living activities in older adults in the community. Sleep. 2005; 28(8):981–989. [PubMed: 16218081]
15. Hjelm C, Stromberg A, Arestedt K, Brostrom A. Association between sleep-disordered breathing, sleep-wake pattern, and cognitive impairment among patients with chronic heart failure. Eur J Heart Fail. 2013; 15(5):496–504. DOI: 10.1093/eurjhf/hft014 [PubMed: 23392278]
16. Jean-Pierre P, Grandner MA, Garland SN, Henry E, Jean-Louis G, Burish TG. Self-reported memory problems in adult-onset cancer survivors: effects of cardiovascular disease and insomnia. Sleep Med. 2015; 16(7):845–849. DOI: 10.1016/j.sleep.2015.02.531 [PubMed: 26026625]
17. Von Ah D, Tallman EF. Perceived cognitive function in breast cancer survivors: evaluating relationships with objective cognitive performance and other symptoms using the functional assessment of cancer therapy-cognitive function instrument. Journal of pain and symptom management. 2015; 49(4):697–706. DOI: 10.1016/j.jpainsymman.2014.08.012 [PubMed: 25240787]
18. Chen ML, Yu CT, Yang CH. Sleep disturbances and quality of life in lung cancer patients undergoing chemotherapy. Lung Cancer. 2008; 62(3):391–400. DOI: 10.1016/j.lungcan.2008.03.016 [PubMed: 18468718]
19. Boonstra L, Harden K, Jarvis S, Palmer S, Kavanaugh-Carveth P, Barnett J, et al. Sleep disturbance in hospitalized recipients of stem cell transplantation. Clinical journal of oncology nursing. 2011; 15(3):271–276. e-pub ahead of print 2011/06/01. DOI: 10.1188/11.CJON.271-276 [PubMed: 21624862]
20. Bevans M, Mitchell S, Marden S. The symptom experience in the first 100 days following allogeneic hematopoietic stem cell transplantation (HSCT). Support Care Cancer. 2008; 16(11): 1243–1254. DOI: 10.1007/s00520-008-0420-6 [PubMed: 18322708]
21. Jim HS, Evans B, Jeong JM, Gonzalez BD, Johnston L, Nelson AM, et al. Sleep disruption in hematopoietic cell transplantation recipients: prevalence, severity, and clinical management. Biol Blood Marrow Transplant. 2014; 20(10):1465–1484. DOI: 10.1016/j.bbmt.2014.04.010 [PubMed: 24747335]
22. Hacker ED, Kapella MC, Park C, Ferrans CE, Larson JL. Sleep Patterns During Hospitalization Following Hematopoietic Stem Cell Transplantation. Oncol Nurs Forum. 2015; 42(4):371–379. DOI: 10.1188/15.ONF.371-379 [PubMed: 26148316]
23. Rischer J, Scherwath A, Zander AR, Koch U, Schulz-Kindermann F. Sleep disturbances and emotional distress in the acute course of hematopoietic stem cell transplantation. Bone Marrow Transplant. 2009; 44(2):121–128. e-pub ahead of print 2009/01/20. DOI: 10.1038/bmt.2008.430 [PubMed: 19151796]
24. Nelson AM, Coe CL, Juckett MB, Rumble ME, Rathouz PJ, Hematti P, et al. Sleep quality following hematopoietic stem cell transplantation: longitudinal trajectories and biobehavioral correlates. Bone Marrow Transplant. 2014; 0 e-pub ahead of print 2014/08/19. doi: 10.1038/bmt.2014.179
25. Rajkumar, SV. Patient information: Multiple myeloma treatment (Beyond the basics). Connor, RF., Kyle, RA., editors. Vol. Topic 690. Waltham, MA: 2016. UpToDateUpToDate
26. Moser NJ, Phillips BA, Guthrie G, Barnett G. Effects of dexamethasone on sleep. Pharmacol Toxicol. 1996; 79(2):100–102. [PubMed: 8878253]

27. Fehm HL, Benkowitsch R, Kern W, Fehm-Wolfsdorf G, Pauschinger P, Born J. Influences of corticosteroids, dexamethasone and hydrocortisone on sleep in humans. Neuropsychobiology. 1986; 16(4):198–204. doi:118326. [PubMed: 3614616]
28. Fortner BV, Stepanski EJ, Wang SC, Kasprowicz S, Durrence HH. Sleep and quality of life in breast cancer patients. Journal of pain and symptom management. 2002; 24(5):471–480. e-pub ahead of print 2003/01/28. [PubMed: 12547047]
29. 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. Journal of pain and symptom management. 2011; 41(5):819–827. e-pub ahead of print 2011/02/11. DOI: 10.1016/j.jpainsymman.2010.07.015 [PubMed: 21306864]
30. Mystakidou K, Parpa E, Tsilika E, Gennatas C, Galanos A, Vlahos L. How is sleep quality affected by the psychological and symptom distress of advanced cancer patients? Palliative medicine. 2009; 23(1):46–53. e-pub ahead of print 2008/10/08. DOI: 10.1177/0269216308098088 [PubMed: 18838488]
31. Fan G, Filipczak L, Chow E. Symptom clusters in cancer patients: a review of the literature. Current oncology. 2007; 14(5):173–179. e-pub ahead of print 2007/10/17. [PubMed: 17938700]
32. Dodd, MJ., Miaskowski, C., Lee, KA. Journal of the National Cancer Institute Monographs. 2004. Occurrence of symptom clusters; p. 76-78.e-pub ahead of print 2004/07/21
33. Donovan KA, Jacobsen PB. Fatigue, depression, and insomnia: evidence for a symptom cluster in cancer. Seminars in oncology nursing. 2007; 23(2):127–135. e-pub ahead of print 2007/05/22. DOI: 10.1016/j.soncn.2007.01.004 [PubMed: 17512440]
34. Theobald DE. Cancer pain, fatigue, distress, and insomnia in cancer patients. Clinical Cornerstone. 2004; 6(1, Supplement D):S15–S21. DOI: 10.1016/S1098-3597(05)80003-1 [PubMed: 15675653]
35. Roscoe JA, Kaufman ME, Matteson-Rusby SE, Palesh OG, Ryan JL, Kohli S, et al. Cancer-related fatigue and sleep disorders. Oncologist. 2007; 12 Suppl 1:35–42. DOI: 10.1634/theoncologist.12-S1-35 [PubMed: 17573454]
36. Ancoli-Israel S, Moore PJ, Jones V. The relationship between fatigue and sleep in cancer patients: a review. Eur J Cancer Care (Engl). 2001; 10(4):245–255. [PubMed: 11806675]
37. Chao, N. Clinical manifestations, diagnosis, and grading of chronic graft-versus-host disease. Negrin, RS., Connor, RF., editors. Vol. Topic 348. Waltham, MA: 2014. UpToDateUpToDate
38. Becker H, Stuifbergen A, Morrison J. Promising New Approaches to Assess Cognitive Functioning in People with Multiple Sclerosis. International journal of MS care. 2012; 14(2):71–76. e-pub ahead of print 2013/04/04. DOI: 10.7224/1537-2073-14.2.71 [PubMed: 23550178]
39. Cancer Survivorship Research: Recovery and Beyond. Washington D.C: 2010. PROMIS: A New Way to Think About Outcome Measurement in Cancer Survivorship.
40. Becker H, Stuifbergen A, Lee H, Kullberg V. Reliability and Validity of PROMIS Cognitive Abilities and Cognitive Concerns Scales Among People with Multiple Sclerosis. International journal of MS care. 2014; 16(1):1–8. DOI: 10.7224/1537-2073.2012-047 [PubMed: 24688349]
41. Stewart, AL., Ware, JE., Brook, RH., Davies, AR. Conceptualization and measurement of health for adults in the Health Insurance Study Vol II Physical health in terms of functioning. The RAND Corporation; Santa Monica, CA: 1978.
42. Hays, RD., Stewart, AL. Sleep Measures. In: Stewart, AL., Ware, JE., editors. Measuring functioning and well-being: The Medical Outcomes Study Approach. Duke University Press; Durham, NC: 1992. p. 235-259.
43. Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in Breast Cancer Survivors: Occurrence, Correlates, and Impact on Quality of Life. Journal of Clinical Oncology. 2000; 18(4):743. [PubMed: 10673515]
44. Smith MT, Wegener ST. Measures of sleep: The Insomnia Severity Index, Medical Outcomes Study (MOS) Sleep Scale, Pittsburgh Sleep Diary (PSD), and Pittsburgh Sleep Quality Index (PSQI). Arthritis care & research. 2003; 49(S5):S184–S196. DOI: 10.1002/art.11409
45. Allen RP, Kosinski M, Hill-Zabala CE, Calloway MO. Psychometric evaluation and tests of validity of the Medical Outcomes Study 12-item Sleep Scale (MOS sleep). Sleep Medicine. 2009; 10(5):531–539. DOI: 10.1016/j.sleep.2008.06.003 [PubMed: 18805054]

46. Hays RD, Martin SA, Sesti AM, Spritzer KL. Psychometric properties of the Medical Outcomes Study Sleep measure. Sleep Medicine. 2005; 6(1):41–44. DOI: 10.1016/j.sleep.2004.07.006 [PubMed: 15680294]
47. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol. 2010; 63(11):1179–1194. DOI: 10.1016/j.jclinepi.2010.04.011 [PubMed: 20685078]
48. Junghaenel DU, Schneider S, Stone AA, Christodoulou C, Broderick JE. Ecological validity and clinical utility of Patient-Reported Outcomes Measurement Information System (PROMIS(R)) instruments for detecting premenstrual symptoms of depression, anger, and fatigue. Journal of psychosomatic research. 2014; 76(4):300–306. e-pub ahead of print 2014/03/19. DOI: 10.1016/j.jpsychores.2014.01.010 [PubMed: 24630180]
49. Broderick JE, Schneider S, Junghaenel DU, Schwartz JE, Stone AA. Validity and reliability of patient-reported outcomes measurement information system instruments in osteoarthritis. Arthritis care & research. 2013; 65(10):1625–1633. DOI: 10.1002/acr.22025 [PubMed: 23592494]
50. Bartlett SJ, Orbai AM, Duncan T, DeLeon E, Ruffing V, Clegg-Smith K, et al. Reliability and Validity of Selected PROMIS Measures in People with Rheumatoid Arthritis. PLoS ONE. 2015; 10(9):e0138543.doi: 10.1371/journal.pone.0138543 [PubMed: 26379233]
51. Cleeland, CS., editor. Measurement of pain by subjective report. Raven Press; New York: 1989.
52. Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain. 1995; 61(2):277–284. e-pub ahead of print 1995/05/01. [PubMed: 7659438]
53. IBM Corp. IBM SPSS Statistics for Windows. 19. Armonk, NY: IBM Corp; 2010.
54. Negrin, RS. Preparative regimens for hematopoietic cell transplantation. Chao, N., Connor, RF., editors. Vol. Topic 3557. Waltham, MA: 2014. UpToDateUpToDate
55. Garland SN, Johnson JA, Savard J, Gehrman P, Perlis M, Carlson L, et al. Sleeping well with cancer: a systematic review of cognitive behavioral therapy for insomnia in cancer patients. Neuropsychiatr Dis Treat. 2014; 10:1113–1124. DOI: 10.2147/NDT.S47790 [PubMed: 24971014]
56. Todd BL, Feuerstein EL, Feuerstein M. When breast cancer survivors report cognitive problems at work. Int J Psychiatry Med. 2011; 42(3):279–294. [PubMed: 22439297]
57. Jacobs SR, Jacobsen PB, Booth-Jones M, Wagner LI, Anasetti C. Evaluation of the Functional Assessment of Cancer Therapy Cognitive Scale with Hematopoetic Stem Cell Transplant Patients. Journal of pain and symptom management. 2007; 33(1):13–23. DOI: 10.1016/j.jpainsymman.2006.06.011 [PubMed: 17196903]
58. Association AP. Diagnostic and statistical manual of mental disorders: DSM-5. American Psychiatric Association; Washington, D.C: 2013.
59. Bower JE. Cancer-related fatigue--mechanisms, risk factors, and treatments. Nat Rev Clin Oncol. 2014; 11(10):597–609. DOI: 10.1038/nrclinonc.2014.127 [PubMed: 25113839]
60. Gielissen MF, Schattenberg AV, Verhagen CA, Rinkes MJ, Bremmers ME, Bleijenberg G. Experience of severe fatigue in long-term survivors of stem cell transplantation. Bone Marrow Transplant. 2007; 39(10):595–603. DOI: 10.1038/sj.bmt.1705624 [PubMed: 17369868]
61. Lee SJ, Joffe S, Kim HT, Socie G, Gilman AL, Wingard JR, et al. Physicians' attitudes about quality-of-life issues in hematopoietic stem cell transplantation. Blood. 2004; 104(7):2194–2200. DOI: 10.1182/blood-2003-07-2430 [PubMed: 15198954]
62. Madsen MT, Huang C, Gögenur I. Actigraphy for measurements of sleep in relation to oncological treatment of patients with cancer: A systematic review. Sleep medicine reviews. 2015; 20:73–83. DOI: 10.1016/j.smrv.2014.07.002 [PubMed: 25155183]
63. Faiz SA, Balachandran D, Hessel AC, Lei X, Beadle BM, William WN Jr, et al. Sleep-related breathing disorders in patients with tumors in the head and neck region. Oncologist. 2014; 19(11):1200–1206. DOI: 10.1634/theoncologist.2014-0176 [PubMed: 25273079]
64. Zhou J, Jolly S. Obstructive sleep apnea and fatigue in head and neck cancer patients. Am J Clin Oncol. 2015; 38(4):411–414. DOI: 10.1097/01.coc.0000436086.61460.cb [PubMed: 24762708]
65. Banno K, Kryger MH. Sleep apnea: Clinical investigations in humans. Sleep Medicine. 2007; 8(4):400–426. DOI: 10.1016/j.sleep.2007.03.003 [PubMed: 17478121]

66. Fleming L, Randell K, Harvey CJ, Espie CA. Does cognitive behaviour therapy for insomnia reduce clinical levels of fatigue, anxiety and depression in cancer patients? Psycho-oncology. 2014; 23(6):679–684. DOI: 10.1002/pon.3468 [PubMed: 24458543]
67. Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part I: Sleep and psychological effects. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005; 23(25): 6083–6096. DOI: 10.1200/JCO.2005.09.548 [PubMed: 16135475]
68. Espie CA, Fleming L, Cassidy J, Samuel L, Taylor LM, White CA, et al. Randomized controlled clinical effectiveness trial of cognitive behavior therapy compared with treatment as usual for persistent insomnia in patients with cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008; 26(28):4651–4658. DOI: 10.1200/JCO. 2007.13.9006 [PubMed: 18591549]
69. Perlis, ML., Jungquist, C., Smith, MT., Posner, D. Cognitive behavioral treatment of insomnia: A session-by-session guide. Springer; New York: 2005.
70. Young JS, Bourgeois JA, Hilty DM, Hardin KA. Sleep in hospitalized medical patients, part 2: behavioral and pharmacological management of sleep disturbances. J Hosp Med. 2009; 4(1):50–59. DOI: 10.1002/jhm.397 [PubMed: 19140196]
71. Mustian KM, Sprod LK, Janelsins M, Peppone LJ, Mohile S. Exercise Recommendations for Cancer-Related Fatigue, Cognitive Impairment, Sleep problems, Depression, Pain, Anxiety, and Physical Dysfunction: A Review. Oncol Hematol Rev. 2012; 8(2):81–88. [PubMed: 23667857]
72. Baumann FT, Zopf EM, Nykamp E, Kraut L, Schüle K, Elter T, et al. Physical activity for patients undergoing an allogeneic hematopoietic stem cell transplantation: benefits of a moderate exercise intervention. European Journal of Haematology. 2011; 87(2):148–156. DOI: 10.1111/j. 1600-0609.2011.01640.x [PubMed: 21545527]
73. Wiskemann J, Dreger P, Schwerdtfeger R, Bondong A, Huber G, Kleindienst N, et al. Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. Blood. 2011; 117(9):2604–2613. DOI: 10.1182/blood-2010-09-306308 [PubMed: 21190995]
74. Jarden M, Nelausen K, Hovgaard D, Boesen E, Adamsen L. The effect of a multimodal intervention on treatment-related symptoms in patients undergoing hematopoietic stem cell transplantation: a randomized controlled trial. Journal of pain and symptom management. 2009; 38(2):174–190. DOI: 10.1016/j.jpainsymman.2008.09.005 [PubMed: 19345060]
75. Harder H, Van Gool AR, Cornelissen JJ, Duivenvoorden HJ, Eijkenboom WMH, Barge RMY, et al. Assessment of pre-treatment cognitive performance in adult bone marrow or haematopoietic stem cell transplantation patients: A comparative study. European Journal of Cancer. 2005; 41(7):1007–1016. http://dx.doi.org/10.1016/j.ejca.2005.01.015. [PubMed: 15862749]
76. Saykin AJ, Wishart HA, Rabin LA, Santulli RB, Flashman LA, West JD, et al. Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. Neurology. 2006; 67(5): 834–842. DOI: 10.1212/01.wnl.0000234032.77541.a2 [PubMed: 16966547]
77. Moul DE, Hall M, Pilkonis PA, Buysse DJ. Self-report measures of insomnia in adults: rationales, choices, and needs. Sleep medicine reviews. 2004; 8(3):177–198. DOI: 10.1016/ S1087-0792(03)00060-1 [PubMed: 15144961]
78. Rollig C, Knop S, Bornhauser M. Multiple myeloma. Lancet. 2015; 385(9983):2197–2208. DOI: 10.1016/S0140-6736(14)60493-1 [PubMed: 25540889]

Table 1

Sample Description (N=138)

Characteristic	% (n)	*M (SD)*	Range
Age		60.4 (9.44)	25-83
Gender (% male)	60.1 (83)		
Race (% Caucasian)	84.8 (117)		
Education (%)			
High school or less	25.3 (35)		
Some college/vocational training	27.5 (38)		
College degree	20.3 (28)		
Graduate or professional training	22.5 (31)		
Unknown	4.3 (6)		
Married or partnered	82.6 (114)		
Employed full or part-time	26.6 (37)		
Type of Transplant			
Autologous	77.5 (107)		
Allogeneic	22.5 (31)		
Diagnosis			
Multiple Myeloma	55.8 (77)		
Non-Hodgkin's Lymphoma	7.2 (10)		
Acute Myeloid Leukemia (AML)	7.2 (10)		
Mantle Cell Lymphoma	5.8 (8)		
Hodgkin's Lymphoma	5.1 (7)		
Other	18.9 (26)		

Note: Other diagnosis include: Blackfan-Diamond Anemia, Burkitt's Lymphoma, CLL, CML, Diffuse Large B-Cell Lymphoma, Follicular Lymphoma, MDS, Myelofibrosis, Myeloproliferative Disorder, Pancytopenia Peripheral T-Cell Lymphoma, Plasmacytoid Dendritic Cell Neoplasm, and T-Cell NHL.

Table 2

Fixed effects for linear mixed models examining change in study variables from pre- to post-transplant

	B	SE	t	p-value	95% CI
Cognitive Problems					
Intercept	18.22	0.78	23.27	<0.01**	16.68, 19.77
Time	0.01	0.10	0.14	0.89	-0.18, 0.21
Transplant type	-0.64	1.65	-0.39	0.70	-3.91, 2.62
Transplant type × time	-0.27	0.233	-1.17	0.25	-0.73,0.19
Sleep Problems					
Intercept	31.27	1.52	20.56	<0.01**	28.26, 34.28
Time	-0.10	0.24	-0.41	0.69	-0.58, 0.38
Transplant type	-1.23	3.21	-0.38	0.70	-7.58, 5.13
Transplant type × time	-0.66	0.56	-1.18	0.24	-1.77, 0.45
Depressive Symptoms					
Intercept	47.51	0.80	59.03	<0.01**	45.92, 49.10
Time	0.04	0.11	0.34	0.74	-0.18, 0.25
Transplant type	-1.61	1.70	-0.95	0.34	-4.97, 1.74
Transplant type × time	0.06	0.25	0.22	0.83	-0.44, 0.55
Fatigue					
Intercept	54.51	0.74	73.95	<0.01**	53.05, 55.97
Time	-0.22	0.11	-1.91	0.06	-0.44, 0.01
Transplant type	-3.23	1.55	-2.08	0.04*	-6.31, -0.16
Transplant type × time	-0.14	0.27	-0.52	0.61	-0.68, 0.40
Pain					
Intercept	2.20	0.19	11.853	<0.01**	1.83, 2.57
Time	-0.19	0.02	-0.89	0.37	-0.06, 0.02
Transplant type	-0.81	0.39	-2.07	0.04*	-1.59, -0.04
Transplant type × time	-0.01	0.05	-0.27	0.79	-0.11, 0.08

Note: Transplant type coded as 0=autologous transplant, 1=allogeneic transplant

* $p < .05$.

** $p<.01$

Table 3

Fixed Effects of Model Predicting Cognitive Functioning

	Beta	SE	*t*	*p*
Intercept	-8.63	2.65	-3.253	<0.01 **
Age	0.06	0.05	1.20	0.23
Transplant -Allogenic	0.17	1.11	0.16	0.88
Time	0.02	0.07	0.34	0.74
Depressive Symptoms	0.31	0.05	6.41	<0.01 **
Fatigue	0.18	0.05	3.84	<0.01 **
Pain	0.05	0.20	0.30	0.77
Sleep Problems	0.07	0.02	3.07	<0.01 **

Note: Transplant type coded as 0=autologous transplant, 1=allogeneic transplant

* $p< .05$.

** $p<.01$