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Sleep Disruption in Hematopoietic Cell Transplant Recipients: Prevalence, Severity, and Clinical Management

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Abstract

Sleep disruption is common among hematopoietic cell transplant (HCT) recipients, with over 50% of patients experiencing sleep disruption pre-transplant, up to 82% experiencing moderate to severe sleep disruption during hospitalization for transplant, and up to 43% in the post-transplant period. These rates of sleep disruption are substantially higher than the general population. Although sleep disruption can be distressing to patients and contribute to diminished quality of life, it is rarely discussed during clinical visits. The goal of the current review is to draw attention to sleep disruption as a clinical problem in HCT in order to facilitate patient education, intervention, and research. The review opens with a discussion of sleep disruption measurement and clinical diagnosis of sleep disorders. An overview of the prevalence, severity, and chronicity of sleep disruption and disorders in patients receiving HCT follows. Current evidence regarding sociodemographic and clinical predictors of sleep disruption and disorders is summarized. The review concludes with suggestions for behavioral and pharmacologic management of sleep disruption and disorders as well as directions for future research.

Keywords

sleep disruption; hematopoietic cell transplant; management of sleep disruption

The number of both autologous and allogeneic hematopoietic cell transplants (HCT) has increased dramatically in recent years, with more than 50,000 performed worldwide each

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year (1). This increase in HCT is due to a greater number of indications for its use as well as advances in therapy, including more frequent use of peripheral blood stem cells, reduced intensity conditioning regimens, greater use of cells from unrelated donors as well as alternative donors, improvements in supportive care, and advances in histocompatibility typing. Survival has generally improved as well (1), resulting in a growing number of patients living with the short- and long-term side effects of HCT.

Sleep disruption is frequently overlooked as a side effect of HCT. Sleep disruption includes difficulty falling asleep, staying asleep, awakening earlier than intended, and/or non-restorative sleep (2). It can occur without a clinical diagnosis of a sleep disorder, although a clinical diagnosis may be warranted if sleep disruption is chronic and impairs daily functioning. Sleep disruption is common after HCT, distressing to patients (3), and associated with greater fatigue and reduced quality of life (3, 4). Nevertheless, sleep disruption is seldom the focus of patient-provider communication. A survey of 180 HCT physicians found that only 17% discussed sleep with their patients during at least half of clinical visits (5).

The goal of the current review is to draw attention to sleep disruption as a clinical problem in HCT and to provide clinicians and researchers with an overview of current evidence in order to facilitate diagnosis, patient education, intervention, and research. The review will start with a brief discussion of the assessment and clinical diagnosis of sleep disruption and common sleep disorders [i.e., insomnia, obstructive sleep apnea (OSA), restless legs syndrome (RLS)]. It will then synthesize and critically review evidence regarding the prevalence, severity, and chronicity of sleep disruption and disorders in patients prior to HCT; during the acute transplant phase; and early, middle, and long-term survivorship. The review will focus on HCT studies published in the past decade to ensure greater relevance to current transplant practices. Sociodemographic and clinical risk factors will be described, with an emphasis on those relevant to HCT. The review will conclude with recommendations for management of sleep disruption and disorders in the transplant setting as well as directions for future research.

Assessment of Sleep Disruption

Objective and self-report measures of sleep disruption have been developed to facilitate differential diagnosis and to monitor sleep over time. The gold standard for objective measurement is polysomnography, which measures multiple biologic processes of sleep, including electrical activity in the brain and heart, limb movement, and eye movements. In addition to collecting essential data for diagnosing sleep disorders, polysomnography allows the additional advantage of monitoring the progression of sleep stages (e.g., rapid eye movement sleep or dreaming) and brain arousal during sleep, which can elucidate the occurrence of sleep interruptions. It is typically conducted in a sleep lab or hospital, although home-based polysomnography is increasingly utilized due to its lower cost. An alternative to polysomnography is actigraphic monitoring, in which a small, non-intrusive piezoelectric monitor similar to a wristwatch is worn on the non-dominant wrist to detect and record motion. Specialized software is used to determine sleep versus waking using algorithms validated against polysomnography. Actigraphy data, in combination with

patients' self-reports of bedtime and rising time, have been found to be a reliable and valid measure of circadian sleep patterns (6). Parameters assessed include time in bed asleep, time until sleep onset, number and length of nighttime awakenings, number and length of daytime naps, as well as circadian variation in sleep and activity. Periodic limb movement can also be assessed. Actigraphs are relatively inexpensive and can be worn at home or in the hospital for several days or weeks, enabling the naturalistic study of sleep disruption over time. Actigraphy is typically used for research rather than diagnostic purposes. Despite the widespread availability of polysomnography and actigraphy, to our knowledge only one study in HCT patients has been published using these measures to assess sleep (7). Thus, objective sleep patterns of HCT patients are largely unknown.

Regarding self-report measures of sleep, several have been validated in cancer patients (8, 9). The most common are the Insomnia Severity Index (ISI) (10) and the Pittsburgh Sleep Quality Index (PSQI) (11). These measures typically ask patients to estimate how long it takes them to fall asleep, how many hours they sleep each night, their use of sleep medications, and their perceptions of sleep quality. Additional measures used include the Epworth Sleepiness Scale (ESS) (12) to evaluate daytime sleepiness and the International Restless Legs Syndrome Study Group rating scale (IRLS) to evaluate RLS symptomatology (13).

In addition to self-report measures, sleep diaries can play an important role in research and clinical diagnosis. Patients are typically asked to fill out the diary on a daily basis for several days or weeks. Requested information includes bedtime and rising times as well as duration of sleep, sleep quality, difficulty initiating and maintaining sleep, daytime napping, medications taken, and other details (14, 15). Diaries can be particularly useful in both the research and clinical settings for obtaining detailed information regarding patterns of disruption, contributing factors, and targets of intervention.

Clinical Diagnosis of Sleep Disorders

Guidelines for clinical evaluation of sleep disorders depend on the disorder under consideration. Regarding insomnia, diagnosis is based on a detailed sleep, medical, substance, and psychiatric history in addition to a physical and mental status examination. Sleep diaries are often used as well. The goal is to establish the type and evolution of insomnia, perpetuating factors, extent of daytime dysfunction, and identification of comorbid medical, substance, and/or psychiatric conditions (16). Diagnostic criteria for insomnia include: 1) difficulty initiating sleep, maintaining sleep, and/or early morning awakening with the inability to return to sleep, 2) significant distress and/or impairment in functioning, 3) sleep difficulty occurs at least 3 nights a week for at least 3 months, 4) sleep difficulty occurs despite adequate opportunity to sleep, and 5) symptoms are not better explained by another mental or medical disorder (2). Regarding OSA, a sleep history and physical exam including symptoms and risk factors (e.g., snoring, gasping/choking at night, daytime sleepiness, obesity, type 2 diabetes, congestive heart failure, treatment-refractory hypertension) are indicated (17). Patients deemed to be at high risk should then be evaluated using polysomnography or home-based monitoring for definitive diagnosis (17). Criteria for diagnosis are 1) evidence by polysomnography of at least five apneas or hypopneas per hour

of sleep (i.e., snoring, snorting/gasping, breathing pauses), 2) daytime sleepiness, fatigue, or unrefreshing sleep despite sufficient opportunity for sleep, 3) symptoms are not better explained by another mental or sleep disorder or medical condition, or 4) evidence by polysomnography of 15 or more obstructive apneas and/or hypopneas per hour of sleep regardless of accompanying symptoms (2). Regarding RLS, diagnosis is based primarily on self-report although polysomnography and actigraphy can be used (18). Diagnostic criteria for RLS are: 1) an urge to move the legs accompanied by or in response to uncomfortable and unpleasant sensations in the legs, 2) the urge begins or worsens during periods of rest or inactivity, is partially or totally relieved by movement, and is worse or occurs only in the evening or at night, 3) symptoms occur at least 3 times a week for 3 months, 4) symptoms are accompanied by significant distress and/or impairment in functioning, and 5) symptoms are not attributable to another mental or medical disorder (2).

Sleep Disruption and Disorders Prior to Transplant

Research on sleep disorders prior to HCT is limited to case studies of lymphomas presenting as OSA [e.g., (19)]. In addition, a study of polysomnography in 12 multiple myeloma patients receiving high-dose chemotherapy (7) reported greater respiratory events and lower-than-normal levels of arterial oxygen saturation, on average. Periodic limb movements in the sample were high and increased during the course of chemotherapy. No studies have reported on the incidence or prevalence of pre-transplant sleep disorders.

There are numerous precipitating factors that can contribute to sleep disruption in patients prior to transplant, however. Patients typically undergo several rounds of standard-dose chemotherapy which is associated with short- and long-term sleep disruption (20). Side effects of chemotherapy, such as peripheral neuropathy, may also contribute to sleep disruption (20). Among cancer patients treated with standard-dose chemotherapy, the prevalence of RLS was 18% (i.e., double that of the general population), with longer chemotherapy associated with greater risk of RLS (21). In addition, many patients have elevated levels of anxiety and depressive symptomatology (22); anxiety can contribute to sleep disruption while both insomnia and hypersomnia are symptoms of depression and share some common etiology (2).

Regarding the prevalence of sleep disruption outside of the context of a diagnosable sleep disorder, 16 studies have examined sleep prior to transplant (see Table 1). Of these, 9 studies did not provide estimates of prevalence of sleep disruption or comparisons to individuals not receiving HCT (7, 23-30). The remaining 7 studies are heterogeneous in terms of their sample composition, sample size, measure of sleep, and clinical cutoff (3, 4, 31-35). Thus, it is not surprising that there is substantial heterogeneity among study findings. Studies utilizing single-item measures of sleep disruption suggest that approximately 8% of autologous patients report moderate to severe sleep disruption (31) while more than 50% of allogeneic patients report sleep disruption of any severity (3). In contrast, the two studies using validated measures [i.e., PSQI, ESS] found that 32% of patients reported clinically-significant sleep disruption before autologous or allogeneic transplant (4) and 43% of multiple myeloma patients reported clinically-significant daytime sleepiness before autologous transplant (35). A direct comparison of sleep disruption between patients

receiving allogeneic versus autologous HCT using a single-item measure suggested that sleep was significantly better among allogeneic patients, although sample sizes were small and findings were confounded by group differences in diagnosis and remission status (33). Comparisons between HCT patient and population norms are mixed, with one large study reporting that patients reported significantly worse sleep prior to autologous transplant or treatment with melphalan or prednisone (32), while two smaller studies have found no differences, perhaps due to low statistical power (33, 34). In summary, although findings are mixed, available data suggest that sleep disruption prior to transplant is common but relatively mild on average.

Sleep Disruption and Disorders During the Acute Transplant Period

The first 100 days post-transplant are typically characterized by multiple acute side effects of the conditioning regimen, including mucositis, enteritis, nausea and emesis, episodes of delirium, and in the case of allogeneic transplant, acute graft versus host disease and immunosuppressive therapies. These side effects and their treatment may disrupt sleep (36). Moreover, these side effects frequently occur in the context of hospitalization, which can have an additive effect on disrupted sleep (4). Consequently, sleep disruption tends to be most pronounced in the first 100 days post-transplant. The most extensive research on sleep disruption in HCT patients has also been conducted during this period (3, 4, 24-26, 30-32, 37-39), although it is characterized by several limitations including small samples which are heterogeneous in terms of diagnosis and transplant type as well as low statistical power. In addition, data are lacking regarding the prevalence and onset of sleep disorders during this time, with the exception of one study reporting a prevalence rate of clinically-significant insomnia of 26% (37). Available data suggest that sleep disruption was the most distressing symptom among allogeneic HCT recipients at day 0 and was significantly correlated with bowel changes and fatigue (3). Sleep disruption significantly increased during the first 100 days, with greatest disruption seen during the conditioning regimen and white blood cell count nadir (31). Mean changes of 27 points on the EORTC QLQ-C30 sleep disruption item were observed from pre-transplant baseline to its peak approximately two weeks post-HCT (25), corresponding to a large increase and effect size of 1.1 standard deviations (SD) (25). These data are consistent with a recent quantitative review of all published studies using the EORTC QLQ-C30 to assess quality of life in HCT patients, which found large increases in sleep disruption during hospitalization (26). Difficulty maintaining sleep was the most common problem in hospitalized HCT patients (82%), followed by non-restorative sleep (61%), problems falling asleep (52%), difficulties falling back to sleep once awake (48%), and early morning awakening (21%) (4). Patients largely attributed these problems to the hospital environment, such as noise from medical equipment and nursing staff, as well as emotional agitation and stress (4, 37). A small study found that allogeneic transplant patients reported better sleep before transplant but worse sleep during hospitalization (4). At the time of hospital discharge, the average severity of sleep disruption among allogeneic and autologous patients was still moderately elevated relative to baseline symptomatology (i.e., . 51 SD) (26). Nevertheless, it appears that increases in sleep disruption are generally transient; by day 100, sleep disruption returns to levels comparable to pre-HCT (4, 25, 31), although these levels are substantially elevated even before the transplant. Patients receiving

allogeneic HCT demonstrate similar levels of sleep disruption near day 100 to patients receiving autologous transplant (4).

Sleep Disruption and Disorders Following the Acute Transplant Period

New precipitating factors of sleep disruption may occur following the acute transplant period. Patients who experienced resolved sleep disruption or never experienced sleep disruption during transplant may develop late-onset sleep problems due to corticosteroid treatment for chronic graft-versus-host disease (GVHD), inflammation due to GVHD or infection, fear of disease progression, pain, or additional treatments for relapsed disease. For example, evidence suggests that long-term corticosteroid use is a risk factor for OSA, perhaps due to weight gain (40). Insomnia is also a common side effects of taking corticosteroids particularly if the medication taken closer to bedtime. Muscle cramps and neuropathy have been found to be common among patients with GVHD and to disrupt sleep (41); neuropathy is also a risk factor for RLS (42). These factors and others can also perpetuate existing sleep problems and contribute to the development of persistent (lasting more than 3 months) or recurrent sleep problems. Additional perpetuating factors of insomnia include cognitive distortions and maladaptive behaviors that begin in reaction to a stressor and persist after the stressor is resolved (43). Examples of cognitive distortions that can make sleep disruption worse are “I’m going to feel terrible tomorrow if I don’t sleep well” or “I’m never going to get to sleep.” Maladaptive behaviors can include spending prolonged time in bed, going to bed excessively early, sleeping late, and staying in bed while no longer asleep. While these behaviors may initially be helpful, particularly for people experiencing acute illness, eventually they can contribute to irregular sleep patterns that result in insomnia long after the patient has recovered from the acute stressor or illness (43).

Only one study has examined the prevalence of sleep disorders after transplant; among 61 allogeneic HCT recipients transplanted 1-10 years previously, 23% met criteria for a diagnosis of insomnia and 3% for hypersomnia; no other sleep disorders were observed (44). In addition, no studies have examined precipitating versus perpetuating factors of sleep disruption following the acute transplant period. Nevertheless, 23 studies have reported on sleep disruption outside the context of a diagnosed sleep disorder 90 days or more after HCT. Notably, 20 assessed sleep using a single item as part of a larger quality of life scale while only 3 included validated measures of sleep. A total of 17 studies were cross-sectional; many included mixed samples of autologous and allogeneic recipients who ranged widely in terms of time from transplant. Thus, definitive conclusions are difficult to draw. However, available data suggest that after peaking during the acute transplant period, the prevalence and severity of sleep disruption remains relatively constant over time. Most studies found no significant change in sleep disruption between one and ten years post-transplant (44-47). HCT survivors tend to report worse sleep disruption compared to population norms and non-cancer comparison groups (i.e., .33-.39 SD) (45, 47-50), but the evidence is mixed (34, 51-53). A cross-sectional study of allogeneic recipients 1-10 years post-transplant found that 23% met criteria for clinical diagnosis of insomnia (44), a rate similar to that of the general population (i.e., 22%) (54). Furthermore, sleep disruption in

patients treated with HCT also does not differ from that in patients treated with standard-dose chemotherapy at 8-9 years post-treatment (55).

Although most evidence suggests no significant change in sleep disruption after the first 100 days post-transplant, estimates of the prevalence of sleep disruption in HCT patients vary widely. At one year post-HCT, 14% of patients receiving allogeneic transplant with reduced intensity conditioning (RIC) and 26% of patients receiving autologous transplant reported sleep disruption (39). A mean of two years after transplant (range 1-3 years), 20% of patients reported sleep disruption (56). In contrast, two to five years after transplant, 49% of patients reported none or slight, 43% reported moderate, and 8% reported severe sleep disruption (46). Five or more years after transplant, 44%, 42%, and 14% of patients reported none or slight, moderate, and severe sleep disruption, respectively (46). A mean of ten years after transplant, 14% reported moderate or severe sleep disruption (52). An average of 13 years after transplant (range 10-18), 81% of patients reported that they were not bothered or only mildly bothered by sleep disruption, while 19% reported they were moderately or severely bothered (57). In summary, the overall prevalence of any sleep problems following the acute transplant period (i.e., after 100 days) ranges from 14-51%, with the prevalence of moderate problems ranging from 14-43% and severe problems ranging from 8-14%. Variability in prevalence rates likely stems from sample bias due to small sample sizes in this literature.

Sociodemographic and Clinical Predictors of Sleep Disruption and Disorders

A clinically-relevant question is how to identify HCT patients at risk of sleep disruption and disorders. Risk factors for insomnia among cancer patients include female gender, anxiety, surgical treatment, and maladaptive beliefs about sleep (58). Among HCT patients, one small study observed that conditioning with busulfan and cyclophosphamide was a risk factor for insomnia (44). Risk factors for OSA in the general population include obesity, type 2 diabetes, congestive heart failure, kidney disease, and treatment-refractory hypertension (17).

Some of the risk factors that lead to sleep disruption and disorders may be more prevalent after HCT (e.g., diabetes, hypertension). Risk factors for RLS in the general population include female gender, pregnancy, low blood ferritin, high alcohol intake, poor renal function, high blood glucose levels, and obesity (42). Although HCT patients are more likely to have high (rather than low) blood ferritin, they may experience high blood glucose levels and weight gain due to treatment with corticosteroids. In addition, several autoimmune diseases are risk factors for RLS (e.g., rheumatoid arthritis, multiple sclerosis, Crohn’s disease), suggesting that high levels of inflammation may play a role (42). These findings have relevance for GVHD as a potential risk factor for RLS, although data are lacking. Thus, in general, risk factors for clinical sleep disorders include female gender, obesity, comorbidities such as diabetes and poor renal function, anxiety, and maladaptive beliefs about sleep.

Regarding sleep disruption outside the context of a diagnosed sleep disorder, there is evidence to suggest that women are more likely to endorse sleep problems than men (44). There is also evidence to suggest that sleep disruption is more severe in older patients (44, 59). Systemic inflammation has been associated with worse sleep, although the sample was small and primarily consisted of autologous HCT recipients (60). Regarding transplant type, allogeneic recipients tend to report better sleep than autologous recipients prior to transplant and 3 years later (33), but worse sleep during the acute transplant period (4, 28, 37). Among allogeneic recipients, significant associations between graft versus host disease (GVHD) and sleep disruption have not been found (47); however, literature examining this relationship is sparse. Other clinical variables, such as bone marrow versus peripheral blood stem cell transplant, have not shown significant differences in the prevalence of sleep problems (61). Nevertheless, comparisons by GVHD and type of hematopoietic stem cell collection are likely underpowered due to small sample sizes. Regarding psychosocial risk factors, research is scarce, but available studies suggest that divorced HCT recipients have higher rates of sleep problems than unmarried patients (29), and unemployed recipients report worse sleep than recipients who are working at the time of assessment (29, 49). In addition, distress, depression, and anxiety are associated with worse sleep (29). Thus, available evidence suggests that risk factors for sleep disruption outside the context of a diagnosed sleep disorder are older age, female gender, divorce, unemployment, distress, and autologous transplant. Additional research is needed to confirm these findings in larger samples.

Treatment of Sleep Disruption and Disorders

Treatments for sleep disorders are varied and depend on the underlying cause. Regarding insomnia, the National Institutes of Health Consensus and the American Academy of Sleep Medicine recommend cognitive behavioral therapy for insomnia (CBT-I) as the standard treatment (18). Extensive research has shown that CBT-I can be as effective as some pharmacological agents in the treatment of insomnia in the general population (62). There have been no studies to date on the effectiveness of CBT-I specifically in patients undergoing HCT. Nevertheless, numerous well-designed studies in cancer patients have shown that CBT-I can indeed be effective in improving objectively (e.g., actigraphy) and subjectively measured (e.g., self-reported insomnia severity and sleep diaries) sleep disruption during and after treatment (63). Therapeutic effects of CBT-I have been found to last for up to 12 months in cancer survivors (63). The American Academy of Sleep Medicine recommends that when pharmacotherapy is used for insomnia, short- or intermediate-acting benzodiazepine receptor agonists (BzRAs) or ramelteon (Rozerem), a melatonin receptor agonist, be prescribed (16). Examples of medications in various drug classes, along with indications, contraindications, and long-term efficacy from randomized placebo-controlled trials in patients with primary insomnia are listed in Table 3. The choice of medications within a class of drugs should depend on patients' symptomatology (e.g., delayed sleep onset vs. difficulty maintaining sleep), patients' preferences regarding use of a controlled substance, and contraindications of the medication. It should be noted that no studies have examined pharmacotherapy for insomnia specifically in the context of HCT.

For OSA, first line treatment is positive airway pressure (PAP) which pneumatically splits the upper airway through a device worn on the nose and/or mouth during sleep (17). Additional therapies for OSA include surgery; oral appliances; implanted upper airway stimulation devices; and behavioral strategies to lose weight, exercise, adjust sleep position, and avoid alcohol and sedatives at bedtime (17). No studies have examined treatments for OSA among patients treated with HCT.

For RLS, first line treatment includes the dopamine agonists pramipexole and ropinirole (18). Additional medication options include levodopa with dopa decarboxylase inhibitor, opioids, gabapentin, enacarbil, and cabergoline. Although no treatment studies for RLS have been conducted specifically among HCT recipients, pregabalin shows promise for treating RLS secondary to neuropathy and/or neuropathic pain (64). There are also data to suggest that some antidepressants may contribute to increased risk of RLS, including citalopram, paroxetine, amitriptyline, mirtazapine, and tramadol, although evidence is mixed (18). Thus, avoidance or discontinuation of use of these medications should be considered in patients with RLS.

To our knowledge, only one behavioral intervention study has been conducted in HCT recipients with the primary aim of improving sleep disruption outside the context of a diagnosed sleep disorder (65). In addition, five behavioral intervention studies have examined sleep disruption as a secondary outcome (66-70). All six studies were randomized trials of psychoeducation, stress management, aerobic exercise, and resistance training alone or in combination during the inpatient period; one study also followed patients for six months post-HCT (66). Samples consisted of patients receiving allogeneic HCT (67, 69) autologous HCT (70), tandem autologous HCT (65), and either allogeneic or autologous HCT (66, 67). All reported null results for sleep disruption compared to usual care. Sample sizes ranged from 42 to 700. Thus, available data suggest that sleep disruption does not improve with exercise or stress management during the inpatient period. Additional studies focusing on long-term transplant survivors are needed.

Discussion

Sleep disruption is a common problem among HCT recipients. In addition to being distressing in its own right, sleep disruption may affect other clinically important outcomes. For example, previous research in patients undergoing standard-dose chemotherapy suggests that sleep disruption occurs first in a cascade of symptoms, contributing to increases in fatigue and in turn, depression (71). In addition, preliminary research suggests that sleep disruption may negatively impact immune response and reconstitution (72), although this has not been demonstrated in the context of HCT. Taken together, these studies argue for early intervention to manage sleep disruption and disorders in HCT recipients.

Effective management of sleep disruption may be difficult in the inpatient setting due to environmental factors that can interrupt sleep. Environmental interventions to improve sleep among inpatients may be more effective than patient-based interventions (e.g., minimizing of nighttime vital signs monitoring). A study conducted by Sharda and colleagues suggests that the vital sign monitoring might not be necessary for HCT patients with low-risk profiles

(i.e., lack of daytime fever and CNS complaints) and may lead to improved sleep and health (73). In contrast, use of an hypnotic (zolpidem) has been associated with increased inpatient falls (74).

Regarding outpatient sleep management, several pharmacologic and behavioral management options are available. National Comprehensive Cancer Network (NCCN) Survivorship guidelines recommend screening for sleep disruption at regular intervals, particularly when there has been a change in clinical status or treatment (75). Insomnia causing decreased daytime functioning, worse quality of life, worsening of complaints, or distress to the patient should be treated with cognitive behavioral therapy, sleep hygiene education, medication, and/or referral to a sleep specialist (75). In light of the strong evidence base for CBT-I in cancer patients, we believe that it should be considered as a first choice for treatment of chronic sleep disruption in HCT recipients. CBT-I lacks side effects, medication interactions, and potential for abuse. In addition, it may be more acceptable than pharmacologic treatment for HCT recipients who would prefer to avoid additional medication. Referral to a clinical psychologist board-certified in behavioral sleep medicine is recommended for patients interested in CBT-I. For patients who are unwilling or unable to engage in CBT-I or for whom it is not effective or feasible, pharmacologic treatment is a viable alternative. Previous research has found that sleep medications commonly prescribed to cancer patients are lorazepam (31.4%) and zolpidem (29.4%) (76), although, as noted previously, no evidence exists for their effectiveness in HCT recipients. Patients with OSA should be referred to a sleep medicine physician, while patients with RLS should be treated with medication and/or referred to a sleep medicine physician (75). Due to the specialized needs of HCT patients, it is advisable that patients with sleep disorders be managed by an interdisciplinary team consisting of the transplant physician, sleep medicine physician, and/or clinical psychologist.

Additional research is clearly needed regarding sleep disruption in HCT recipients. Longitudinal studies should be conducted to determine prevalence, chronicity, and natural course of sleep disruption and disorders secondary to HCT using well-validated objective and self-report measures of sleep as well as clinical diagnostic criteria. The prevalence of sleep disruption and disorders in HCT recipients should be compared to population normative data, as they are also common among individuals without cancer. Future studies should also aim to identify genetic, sociodemographic, and clinical risk factors for sleep disruption and disorders secondary to HCT. Well-designed randomized controlled trials are needed to test the efficacy of behavioral and pharmaceutical management of sleep problems in HCT recipients.

In summary, sleep disruption is a common, distressing, and under-recognized problem among HCT recipients. Clinical efforts to proactively manage sleep disruption and disorders have the potential to improve overall quality of life in this population. Until more research is conducted with a specific focus on HCT recipients, strategies to manage sleep disruption and disorders should be adapted from the current evidence base in cancer patients and the general population.

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References

1. Pasquini MC, Wang Z, Horowitz MM, Gale RP. 2010 report from the Center for International Blood and Marrow Transplant Research (CIBMTR): current uses and outcomes of hematopoietic cell transplants for blood and bone marrow disorders. Clin Transpl. 2010:87–105. [PubMed: 21696033]
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. American Psychiatric Association; Washington D.C.: 2013.
3. Bevans MF, Mitchell SA, Marden S. The symptom experience in the first 100 days following allogeneic hematopoietic stem cell transplantation (HSCT). Support Care Cancer. 2008; 16:1243–1254. [PubMed: 18322708]
4. 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; 44:121–128. [PubMed: 19151796]
5. Lee SJ, Joffe S, Kim HT, et al. Physicians' attitudes about quality-of-life issues in hematopoietic stem cell transplantation. Blood. 2004; 104:2194–2200. [PubMed: 15198954]
6. Morgenthaler T, Alessi C, Friedman L, et al. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. Sleep. 2007; 30:519–529. [PubMed: 17520797]
7. Enderlin CA, Coleman EA, Davila D, et al. Sleep measured by polysomnography in patients receiving high-dose chemotherapy for multiple myeloma prior to stem cell transplantation. Oncology nursing forum. 2013; 40:73–81. [PubMed: 23269772]
8. 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; 27:140–148. [PubMed: 15157038]
9. Savard MH, Savard J, Simard S, Ivers H. Empirical validation of the Insomnia Severity Index in cancer patients. Psychooncology. 2005; 14:429–441. [PubMed: 15376284]
10. Morin, CM. Insomnia: Psychological assessment and mangement. Guilford Press; New York: 1993.
11. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989; 28:193–213. [PubMed: 2748771]
12. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991; 14:540–545. [PubMed: 1798888]
13. Walters AS, LeBrocq C, Dhar A, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep medicine. 2003; 4:121–132. [PubMed: 14592342]
14. Monk TH, Reynolds CF 3rd, Kupfer DJ, et al. The Pittsburgh Sleep Diary. Journal of sleep research. 1994; 3:111–120.
15. Calloway M, Bharmal M, Hill-Zabala C, Allen R. Development and validation of a subjective post sleep diary (SPSD) to assess sleep status in subjects with restless legs syndrome. Sleep medicine. 2011; 12:704–710. [PubMed: 21733752]
16. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2008; 4:487–504. [PubMed: 18853708]
17. Epstein LJ, Kristo D, Strollo PJ Jr. et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2009; 5:263–276. [PubMed: 19960649]

18. Aurora RN, Kristo DA, Bista SR, et al. The treatment of restless legs syndrome and periodic limb movement disorder in adults-an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. Sleep. 2012; 35:1039–1062. [PubMed: 22851801]
19. Tsou YA, Cheng YK, Lin CD, Chang WC, Tsai MH. Small B cell lymphocytic lymphoma presenting as obstructive sleep apnea. World journal of surgical oncology. 2004; 2:26. [PubMed: 15282026]
20. Hjorth M, Hjertner O, Knudsen LM, et al. Thalidomide and dexamethasone vs. bortezomib and dexamethasone for melphalan refractory myeloma: a randomized study. European journal of haematology. 2012; 88:485–496. [PubMed: 22404182]
21. Ostacoli L, Saini A, Ferini-Strambi L, et al. Restless legs syndrome and its relationship with anxiety, depression, and quality of life in cancer patients undergoing chemotherapy. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2010; 19:531–537.
22. Sherman AC, Simonton S, Latif U, Plante TG, Anaissie EJ. Changes in quality-of-life and psychosocial adjustment among multiple myeloma patients treated with high-dose melphalan and autologous stem cell transplantation. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2009; 15:12–20.
23. Frick E, Ramm G, Bumeder I, et al. Social support and quality of life of patients prior to stem cell or bone marrow transplantation. British journal of health psychology. 2006; 11:451–462. [PubMed: 16870055]
24. Danaher EH, Ferrans C, Verlen E, et al. Fatigue and physical activity in patients undergoing hematopoietic stem cell transplant. Oncol Nurs Forum. 2006; 33:614–624. [PubMed: 16676017]
25. Frodin U, Borjeson S, Lyth J, Lotfi K. A prospective evaluation of patients' health-related quality of life during auto-SCT: a 3-year follow-up. Bone Marrow Transplant. 2011; 46:1345–1352. [PubMed: 21113189]
26. Grulke N, Albani C, Bailer H. Quality of life in patients before and after haematopoietic stem cell transplantation measured with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire QLQ-C30. Bone Marrow Transplant. 2011
27. Hacker ED, Larson JL, Peace D. Exercise in patients receiving hematopoietic stem cell transplantation: lessons learned and results from a feasibility study. Oncology nursing forum. 2011; 38:216–223. [PubMed: 21356659]
28. Cohen MZ, Rozmus CL, Mendoza TR, et al. Symptoms and quality of life in diverse patients undergoing hematopoietic stem cell transplantation. Journal of pain and symptom management. 2012; 44:168–180. [PubMed: 22699091]
29. Gruber U, Fegg M, Buchmann M, Kolb HJ, Hiddemann W. The long-term psychosocial effects of haematopoetic stem cell transplantation. Eur J Cancer Care (Engl). 2003; 12:249–256. [PubMed: 12919304]
30. Hacker ED, Ferrans CE. Quality of life immediately after peripheral blood stem cell transplantation. Cancer nursing. 2003; 26:312–322. [PubMed: 12886122]
31. Anderson KO, Giralt SA, Mendoza TR, et al. Symptom burden in patients undergoing autologous stem-cell transplantation. Bone Marrow Transplant. 2007; 39:759–766. [PubMed: 17438588]
32. Gulbrandsen N, Hjermstad MJ, Wisloff F. Interpretation of quality of life scores in multiple myeloma by comparison with a reference population and assessment of the clinical importance of score differences. Eur J Haematol. 2004; 72:172–180. [PubMed: 14962235]
33. Hjermstad MJ, Knobel H, Brinch L, et al. A prospective study of health-related quality of life, fatigue, anxiety and depression 3-5 years after stem cell transplantation. Bone Marrow Transplant. 2004; 34:257–266. [PubMed: 15170167]
34. Wettergren L, Sprangers M, Bjorkholm M, Langius-Eklof A. Quality of life before and one year following stem cell transplantation using an individualized and a standardized instrument. Psychooncology. 2008; 17:338–346. [PubMed: 17614094]
35. Sherman AC, Coleman EA, Griffith K, et al. Use of a supportive care team for screening and preemptive intervention among multiple myeloma patients receiving stem cell transplantation.

Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2003; 11:568–574. [PubMed: 12827482]

36. Stiff PJ, Emmanouilides C, Bensinger WI, et al. Palifermin reduces patient-reported mouth and throat soreness and improves patient functioning in the hematopoietic stem-cell transplantation setting. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2006; 24:5186–5193. [PubMed: 16391299]
37. Boonstra L, Harden K, Jarvis S, et al. Sleep disturbance in hospitalized recipients of stem cell transplantation. Clin J Oncol Nurs. 2011; 15:271–276. [PubMed: 21624862]
38. Gulbrandsen N, Wisloff F, Brinch L, et al. Health-related quality of life in multiple myeloma patients receiving high-dose chemotherapy with autologous blood stem-cell support. Med Oncol. 2001; 18:65–77. [PubMed: 11778972]
39. Diez-Campelo M, Perez-Simon JA, Gonzalez-Porras JR, et al. Quality of life assessment in patients undergoing reduced intensity conditioning allogeneic as compared to autologous transplantation: results of a prospective study. Bone Marrow Transplant. 2004; 34:729–738. [PubMed: 15354204]
40. Berger G, Hardak E, Shaham B, Avitan E, Yigla M. Preliminary prospective explanatory observation on the impact of 3-month steroid therapy on the objective measures of sleep-disordered breathing. Sleep & breathing = Schlaf & Atmung. 2012; 16:549–553. [PubMed: 21755279]
41. Kraus PD, Wolff D, Grauer O, et al. Muscle cramps and neuropathies in patients with allogeneic hematopoietic stem cell transplantation and graft-versus-host disease. PloS one. 2012; 7:e44922. [PubMed: 23028681]
42. Yeh P, Walters AS, Tsuang JW. Restless legs syndrome: a comprehensive overview on its epidemiology, risk factors, and treatment. Sleep & breathing = Schlaf & Atmung. 2012; 16:987–1007. [PubMed: 22038683]
43. Palesh O, Peppone L, Innominato PF, et al. Prevalence, putative mechanisms, and current management of sleep problems during chemotherapy for cancer. Nat Sci Sleep. 2012; 4:151–162. [PubMed: 23486503]
44. Faulhaber GA, Furlanetto TW, Astigarraga CC, et al. Association of busulfan and cyclophosphamide conditioning with sleep disorders after hematopoietic stem cell transplantation. Acta Haematol. 2010; 124:125–128. [PubMed: 20861613]
45. Hendriks MG, Schouten HC. Quality of life after stem cell transplantation: a patient, partner and physician perspective. Eur J Intern Med. 2002; 13:52–56. [PubMed: 11836083]
46. Worel N, Biener D, Kalhs P, et al. Long-term outcome and quality of life of patients who are alive and in complete remission more than two years after allogeneic and syngeneic stem cell transplantation. Bone Marrow Transplant. 2002; 30:619–626. [PubMed: 12407437]
47. Pallua S, Giesinger J, Oberguggenberger A, et al. Impact of GvHD on quality of life in long-term survivors of haematopoietic transplantation. Bone Marrow Transplant. 2010; 45:1534–1539. [PubMed: 20228854]
48. Andrykowski MA, Bishop MM, Hahn EA, et al. Long-term health-related quality of life, growth, and spiritual well-being after hematopoietic stem-cell transplantation. J Clin Oncol. 2005; 23:599–608. [PubMed: 15659507]
49. Bieri S, Roosnek E, Helg C, et al. Quality of life and social integration after allogeneic hematopoietic SCT. Bone Marrow Transplant. 2008; 42:819–827. [PubMed: 18711345]
50. Bishop MM, Beaumont JL, Hahn EA, et al. Late effects of cancer and hematopoietic stem-cell transplantation on spouses or partners compared with survivors and survivor-matched controls. J Clin Oncol. 2007; 25:1403–1411. [PubMed: 17416860]
51. Kopp M, Holzner B, Meraner V, et al. Quality of life in adult hematopoietic cell transplant patients at least 5 yr after treatment: a comparison with healthy controls. Eur J Haematol. 2005; 74:304–308. [PubMed: 15777342]
52. Syrjala KL, Langer SL, Abrams JR, Storer BE, Martin PJ. Late effects of hematopoietic cell transplantation among 10-year adult survivors compared with case-matched controls. J Clin Oncol. 2005; 23:6596–6606. [PubMed: 16170167]

53. Hayden PJ, Keogh F, Ni Conghaile M, et al. A single-centre assessment of long-term quality-of-life status after sibling allogeneic stem cell transplantation for chronic myeloid leukaemia in first chronic phase. Bone Marrow Transplant. 2004; 34:545–556. [PubMed: 15343272]
54. Roth T, Coulouvrat C, Hajak G, et al. Prevalence and perceived health associated with insomnia based on DSM-IV-TR; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; and Research Diagnostic Criteria/International Classification of Sleep Disorders, Second Edition criteria: results from the America Insomnia Survey. Biol Psychiatry. 2011; 69:592–600. [PubMed: 21195389]
55. Messerer D, Engel J, Hasford J, et al. Impact of different post-remission strategies on quality of life in patients with acute myeloid leukemia. Haematologica. 2008; 93:826–833. [PubMed: 18469349]
56. Mosher CE, DuHamel KN, Rini C, et al. Quality of life concerns and depression among hematopoietic stem cell transplant survivors. Support Care Cancer. 2011; 19:1357–1365. [PubMed: 20661753]
57. Kiss TL, Abdolell M, Jamal N, et al. Long-term medical outcomes and quality-of-life assessment of patients with chronic myeloid leukemia followed at least 10 years after allogeneic bone marrow transplantation. J Clin Oncol. 2002; 20:2334–2343. [PubMed: 11981005]
58. 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. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009; 27:5233–5239. [PubMed: 19738124]
59. Watson M, Buck G, Wheatley K, et al. Adverse impact of bone marrow transplantation on quality of life in acute myeloid leukaemia patients; analysis of the UK Medical Research Council AML 10 Trial. Eur J Cancer. 2004; 40:971–978. [PubMed: 15093571]
60. Boland E, Eiser C, Ezaydi Y, et al. Living with advanced but stable multiple myeloma: a study of the symptom burden and cumulative effects of disease and intensive (hematopoietic stem cell transplant-based) treatment on health-related quality of life. J Pain Symptom Manage. 2013; 46:671–680. [PubMed: 23535325]
61. Gallardo D, de la Camara R, Nieto JB, et al. Is mobilized peripheral blood comparable with bone marrow as a source of hematopoietic stem cells for allogeneic transplantation from HLA-identical sibling donors? A case-control study. Haematologica. 2009; 94:1282–1288. [PubMed: 19734420]
62. NIH State-of-the-Science Conference Statement on manifestations and management of chronic insomnia in adults. NIH Consens State Sci Statements. 2005; 22:1–30.
63. 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; 23:6083–6096. [PubMed: 16135475]
64. Sommer M, Bachmann CG, Liebetanz KM, et al. Pregabalin in restless legs syndrome with and without neuropathic pain. Acta neurologica Scandinavica. 2007; 115:347–350. [PubMed: 17489946]
65. Coleman EA, Goodwin JA, Kennedy R, et al. Effects of exercise on fatigue, sleep, and performance: a randomized trial. Oncol Nurs Forum. 2012; 39:468–477. [PubMed: 22940511]
66. Lee, SJ.; Le Rademacher, J.; Jim, HS., et al. American Society of Hematology. New Orleans: 2013. Exercise and stress management training for patients undergoing autologous or allogeneic hematopoietic cell transplantation: Results from Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0902. 2013
67. Baumann FT, Kraut L, Schule K, Bloch W, Fauser AA. A controlled randomized study examining the effects of exercise therapy on patients undergoing haematopoietic stem cell transplantation. Bone marrow transplantation. 2010; 45:355–362. [PubMed: 19597418]
68. Baumann FT, Zopf EM, Nykamp E, et al. Physical activity for patients undergoing an allogeneic hematopoietic stem cell transplantation: benefits of a moderate exercise intervention. European journal of haematology. 2011; 87:148–156. [PubMed: 21545527]
69. Jarden M, Baadsgaard MT, Hovgaard DJ, Boesen E, Adamsen L. A randomized trial on the effect of a multimodal intervention on physical capacity, functional performance and quality of life in adult patients undergoing allogeneic SCT. Bone marrow transplantation. 2009; 43:725–737. [PubMed: 19234513]

70. Oechsle K, Aslan Z, Suesse Y, et al. Multimodal exercise training during myeloablative chemotherapy: a prospective randomized pilot trial. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2014; 22:63–69. [PubMed: 23989498]
71. Jim HS, Jacobsen PB, Phillips KM, et al. Lagged Relationships Among Sleep Disturbance, Fatigue, and Depressed Mood During Chemotherapy. Health Psychol. 2013
72. Guariniello LD, Vicari P, Lee KS, de Oliveira AC, Tufik S. Bone marrow and peripheral white blood cells number is affected by sleep deprivation in a murine experimental model. J Cell Physiol. 2012; 227:361–366. [PubMed: 21437906]
73. Sharda S, Carter J, Wingard JR, Mehta P. Monitoring vital signs in a bone marrow transplant unit: are they needed in the middle of the night? Bone marrow transplantation. 2001; 27:1197–1200. [PubMed: 11551031]
74. Kolla BP, Lovely JK, Mansukhani MP, Morgenthaler TI. Zolpidem is independently associated with increased risk of inpatient falls. J Hosp Med. 2013; 8:1–6. [PubMed: 23165956]
75. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology Survivorship Version 1.2013.
76. Costantini C, Ale-Ali A, Helsten T. Sleep aid prescribing practices during neoadjuvant or adjuvant chemotherapy for breast cancer. J Palliat Med. 2011; 14:563–566. [PubMed: 21388255]
77. De Souza CA, Duraes MI, Vigorito AC, et al. Quality of life in patients randomized to receive a bone marrow or a peripheral blood allograft. Haematologica. 2002; 87:1281–1285. [PubMed: 12495902]
78. Hacker ED, Ferrans CE. Quality of life immediately after peripheral blood stem cell transplantation. Cancer Nurs. 2003; 26:312–322. [PubMed: 12886122]
79. Harder H, Cornelissen JJ, Van Gool AR, et al. Cognitive functioning and quality of life in long-term adult survivors of bone marrow transplantation. Cancer. 2002; 95:183–192. [PubMed: 12115332]
80. Staff, P. Physicians' Desk Reference 2013. 67 edPDR Network; Montvale, NJ: 2012.

Table 1

Observational Studies of Sleep in Hematopoietic Cell Transplant Recipients

Study	Sample	Demographics	Time Frame	Sleep Measures	Statistical Analyses	Main Relevant Findings
Anderson et al. (2007) (31)	Auto HCT (N=100) Included both disease free & relapsed patients NHL (34%), MM (66%)	Age: Mean = 53.6 (9.7) Range = 24-75 Gender: M = 60% F = 40% Race: Caucasian = 81% African American = 12% Hispanic = 5% Other = 2%	Longitudinal; 5 assessments: Pre-HCT, 3rd-4th day of conditioning, day 0, nadir, day 30)	MDASI-BMT (a single item measure of sleep disruption)	Repeated Measures ANOVA	The percentage of patients reporting disturbed sleep at moderate or severe levels at each time point were as follows: 8% at baseline, 34% at conditioning, 39% at nadir, 14% at day 30. 8 % reported sleep disruption at baseline, 34% at conditioning, 26% at transplant, 39% at nadir and14% at day 30. Sleep disruption was one of most severe symptoms at nadir, returned to pre-HCT levels by day 30 post-HCT Sleep disruption was significantly worse for NHL than MM patients (p=.024)
Andrykowski et al. (2005) (48)	HCT survivors (N=662) & age- and sex-matched healthy controls (N=158) Allo (41%), Auto (59%), Missing (1%) AML (29%), CML (19%), ALL (7%), Breast cancer (23%), Lymphoma (20%), Other (1%)	Mean Age: 50.1 (14.2) Gender: M = 30% Race: White = 95%	Cross-sectional; Mean of 7 years (84 months) post-HCT (inclusion criteria: >12mo post-HCT)	MOS-Sleep	MANOVA (univariate analyses)	HCT survivor group reported more sleep problems than healthy control group (effect size = .39, p<.001).
Bevans et al. (2008) (3)	Allo HCT (N=76) RIC (54%), Myeloablative (46%) Included patients in remission and with progressive disease Acute leukemia (17%), Chronic leukemia (38%), Lymphoma or MM (29%), MDS (12%), Non-hematological malignancy (4%)	Mean Age: 40.2 (13.5) Gender: M: = 67% F: = 33% Race: Caucasian = 46% Hispanic = 30% Asian = 9% Black = 7% Other = 8%	Longitudinal; Baseline (before transplant conditioning), Day 0, Day 30, Day 100	Symptom Distress Scale	Univariate descriptive analyses	At baseline, approximately 55% of patients reported insomnia, 86% had insomnia at day 0, nearly 70 % had insomnia at day 30 and at day 100, insomnia levels went down to baseline levels. Insomnia was the most distressing symptom at day 0 (reported by 32% of participants).
Bieri et al. (2008) (49, 50)	Allo HCT (N=124) AML (n=40), ALL (n=20), CML (n=31), CLL (n=1), MDS (n=8), Lymphoma (n=14), MM (n=1), MPS (n=3), AA (n=6)	Age: Median = 34 Range = 14-65 Gender: M = 79 F = 45	Cross-sectional; Median of 7.3 years post-HCT	EORTC QLQ-C30	Descriptive statistics, t-test	Significantly higher sleep disruption among HCT patients compared to Norwegian population norms. Unclear where normative data came from. Difference of .33 SD. Univariate analysis indicated that employment status was associated with sleep disruption.
Bishop et al. (2007) (50)	HCT (N=177), Partners (N=177), Controls (N=133) Allogeneic=78 (44%), Autologous=99 (56%)	Mean Age: 50 (10) Gender: F = 50%	Cross-sectional; Mean of 7 years (84 months) post-HCT (inclusion criteria:	MOS-Sleep	Mixed Effect Linear Models	Patients showed significantly higher rates of sleep problems than controls (ES=.39).

Study	Sample	Demographics	Time Frame	Sleep Measures	Statistical Analyses	Main Relevant Findings
	AML or ALL (39%), CML (22%), Breast cancer (18%), Lymphoma (21%)	Race: White = 94%	>12mo post-HCT)			Partners showed significantly higher rates of sleep problems than controls (ES=.22).
Boland et al. (2013) (60)	Auto HCT (n=29), Allo HCT (n=3), Tandem HCT (n=10) MM (100%) MEL (n=29), maintenance lenalidomide (n=3), maintenance interferon alpha (n=1)	Age: Median: 60 Range: 41-71 Gender: M = 17 F = 15	Cross-sectional: Mean 5.5 years post-diagnosis (range 2-12)	EORTC QLQ C-30	Spearman's correlations	Sleep disruption significantly correlated with serum IL-6 levels (p=.02)
Boonstra et al. (2011) (37)	Hospitalized HCT (N=69) Allo (n=46), Auto (n=23) Disease sites not reported	Gender: Male = 41 Female = 26	Cross-sectional; Day14 post-HCT (reflective of 2 week period)	ISI	Descriptives and Chi-Square tests	No insomnia = 26%, subthreshold insomnia = 48%, Clinically significant insomnia (moderate) = 23%, Clinically significant insomnia (severe) = 3%. Female and allo patients were more likely to report insomnia (no observed differences in age). Toileting (85%), staff interruptions (80%), physical symptoms (41%), anxiety-self (39%), anxiety-others (35%), & noise (24%) most common reasons for sleep disruption.
Cohen et al. (2012) (28)	Diverse HCT (N=164) Allo (62%), Auto (38%) Disease sites not reported HD (n=24), NHL (n=21), AML (n=11) 38 Chemo, 20 Radiochemo	Mean Age: 45 Range = 19-74 Gender: M = 56% F = 44% Race: Black = 15% Latino = 23% Caucasian = 62%	Longitudinal; 8 assessments: Pre-HCT – Day 100 post-HCT	MDASI	Longitudinal Linear Mixed Models, Correlations	Sleep disruption was one of the five worst reported symptoms; associated with myeloablative regimens and worse functional status.
Danaher et al. (2006) (24)	HCT (N=20 at baseline; N=17 post-HCT) Auto =10 (59%), Allo = 7 (41%) Lymphoma (23%), CML (6%), AML (18%), ALL (6%), MM (29%), Myelofibrosis (12%), Plasma cell leukemia (6%)	Mean age: 48.65 (23-64) Gender: M = 45% F = 55% Race: Caucasian = 35%, Black = 40%, Latino = 15%, Asian = 5%, Other = 5%	Longitudinal; Pre-HCT & 5 days & 8 days post-HCT	EORTC QLQ-C30	t-tests	Sleep disruption significantly worse post-HCT.
De Souza et al. (2002) (77)	Allo HCT (N=26) All in complete remission BM (n=13), PBSC (n=13) CML (n=21), AML (n=3), MDS (n=1), ALL (n=1)	Age: Range = 19-61 Gender: M = 14 F = 12	Cross-sectional; Mean of 1248 days post-HCT	WHOQOL-100: Single item assessment: "Do you have difficulties with sleeping?"	Wilcoxon rank sum, Kruskal-Wallis' tests	No differences in sleep between patients receiving BM versus PBSC.

Study	Sample	Demographics	Time Frame	Sleep Measures	Statistical Analyses	Main Relevant Findings
Diez-Campelo et al. (2004) (39)	RIC Allo HCT (n=47), Auto HCT (n=70) AML (n=15), ALL (n=3), CML (n=5), MDS (n=7), NHL (n=3), HD (n=11), Breast cancer (n=6), MM (n=29), CLL (n=4), Amyloidosis (n=1) FLU/MEL or FLU/BU (n=47), BEAM (n=37), BU/MEL (n=8), CY/ carboplatin/thiotepa (n=6), MEL (n=11), BU/CY (n=7), CY/TBI (n=1)	Age Range = 16-70	Longitudinal; 6 assessments: days +7, +14, +21, +90, +270, +360 post-HCT	FACT sleep disruption item: “I am sleeping well”	Descriptives	14.3% of allo-RIC and 26.3% of auto patients had problems sleeping at one year post-transplant (p=.29).
Enderlin et al. (2013) (7)	Auto HCT (N=12) MM only All participants on the Total Therapy 3 protocol	Age: Mean = 61 Range = 48-72 Gender: M = 10 F = 2 Race: Caucasian = 10 African American = 2	Cross-sectional; Pre-HCT (one assessment prior to, one assessment after chemo cycle)	Polysomnography	Descriptives	Patients had a short sleep time, excessive time spent awake after sleep onset, poor sleep efficiency, more time in non-REM sleep, low arterial oxygen saturation, elevated periodic limb movements as measured by polysomnography.
Faulhaber et al. (2010) (44)	Allo HCT (N=61) CML (37.7%), Severe AA (21.3%), AML (14.7), ALL (8.1%), NHL (6.5%), HD (4.9%), Other (6.5%) BU/CY (65.6%), RIC (18%), Cy (9.8%), TBI/CY (6.6%)	Mean Age: 36.5 (12.3) Gender: M = 54.1% F = 45.9%	Cross-sectional; 1 – 10 years post-HCT	DSM-IV-TR criteria for sleep disorders	multivariate analysis	The prevalence of sleep disorders was 26.2%. Multivariate analysis indicated that busulfan-cyclophosphamide was an independent risk factor for sleep disorders (included sex & age).
Frick et al. (2006) (23)	HCT (N=282) Allo (35%), Auto (62%) AML/MDS (11.7%), ALL (5%), CML (16%), HD (4.3%), NHL (29.9%), MM (29.5%), Other (3.6%); (97% hematological malignancies)	Age: Median = 48.5 SD=11.9 Gender: F = 39%	Cross-sectional; Pre-HCT	EORTC QLQ-C30	Pearson’s Correlation Coefficient	Compared patients to sample of German population – 36.6 patients versus 16.4 population (no SDs or SEs given). Sleep disruption was positively correlated with problematic social support (.183)
Frodin et al. (2011) (25)	Auto HCT (N=111) MM (n=56), Lymphoma (n=32), Testicular cancer (n=3), AML (n=2), Multiple sclerosis (n=1) Conditioning: MEL (n=56), BEAM (n=33), CEC (n=3), BU/MEL (n=2), ZAM (Aavados, ARA-C, Melphalan) (n=2)	Based on 96 of the patients: Age: Mean = 54 (12) Gender: M = 62 F = 34	Longitudinal; Baseline, Week 1, Week 2, Week 3, Week 4, Month 2, Month 3, Month 6, Year 1, Year 1.5, Year 2, Year 2.5, & Year 3	EORTC QLQ-C30	The results are presented using descriptive statistics, means adjusted for gender and age	Worst sleep disruption at 2 weeks post-HCT. Sleep returned to baseline levels by 2 months post-HCT, and remained relatively stable thereafter through the 3 year follow up. Increase of 1.1 SD from pre-HCT baseline to 2 week follow up. Sleep disruption did not differ between myeloma and lymphoma patients.
Gallardo et al. (2009)(61)	Allogeneic BMT (N=820; N=150 QOL assessed) Peripheral Blood Group (N=410): AML(25.9%), ALL (24.1%), CML (30.7%), MM (2.7%), NHL (7.3%), HD (0.5%), MDS (7.8%), Other (1%)	Peripheral Blood Group (N=410): Age: Median = 35 Range = 15-59 Gender:	Retrospective; Follow up for alive patients: Median 43.8 months for patients receiving peripheral blood, Median 46.6	EORTC QLQ-C30, Spanish Version	Chi-square, t tests	There were no significant differences in sleep difficulties reported between patients who received bone marrow (n=73, M=15.9, SD=26.7) versus peripheral blood (n=77, M=18.2,

Study	Sample	Demographics	Time Frame	Sleep Measures	Statistical Analyses	Main Relevant Findings
	Bone Marrow Group (N=410): AML (25.9%), ALL (24.1%), CML (30.7%), MM (2.7%), NHL (7.3%), HD (0.5%), MDS (7.8%), Other (1%) Peripheral Blood Group: Conditioning regimen with TBI=198 (48.3%) Bone Marrow Group: Conditioning regimen with TBI=200 (48.8%)	M = 58.9% F = 41.1% Bone Marrow Group (N=410): Age: Median = 35 Range = 15-59 Gender: M = 62.3% F = 37.7%	months for patients receiving bone marrow.			SD=26.2).
Gruber et al. (2003) (29)	HCT (N=163) Allo (85%), Auto (12%), Syngenic (3%) Included both disease free & relapsed patients CLL/CML (n=69), ALL/AML (n=58), Other (n=36)	Age at BMT: Median = 34 (9.2) Gender: M = 62.6% F = 37.4%	Cross-sectional; Within 16 years post-HCT; (inclusion criteria: ≥2yrs post-HCT, transplanted b/w 1979 - 1996)	SF-36, EORTC QLQ-C30, SIP, Herschbach Stress in Cancer Patients	Mann–Whitney analysis, correlations	Unemployed, divorced, and distressed patients reported significantly greater sleep problems.
Grulke et al. (2011) (26)	Quantitative review of 33 papers reporting EORTC scores in HCT and covering 2800 patients Range of participants (15-415), Total N=2804 Allo=52.6% Auto=48.4% Acute leukemia (28%), CML (15.3%), other hemaological diseases (42.1%), solid tumors (14.8%)	Age Range (14-70) Gender: M = 50.1%	Longitudinal; Pre-HCT, During Hospitalization, At Discharge, Up to 6 months, 7-12 months, 1-3 years, >3 years	EORTC QLQ-C30	Categorized data by time of assessment, unweighted arithmetic means.	Sleep problems increase during inpatient stay then return to baseline levels following discharge (change of 25 points). Sleep problems described by authors as “persistent” and at a “high level”.
Gulbrandsen et al. (2004) (32)	Auto HCT (N=274) MEL/Prednisone only (n=203), MM only	Not reported	Longitudinal; Pre-HCT, 1 month, 6 months, 12 months, 24 months, & 36 months post-HCT	EORTC QOLQ-C30	Linear Regression model with forward stepwise selection	Reference population of population-based study of 3000 Norwegians aged 18-93 years Statistically significant difference between newly diagnosed multiple myeloma patients and population norms, small in magnitude with worse scores in patients.
Hacker et al. (2003) (78)	HCT (Pre-HCT N=16, 6 Weeks post-discharge N=8) Allo (n=11), Auto (n=5) Lymphoma (n=4), CML (n=3), AML (n=3), ALL (n=1), MM (n=3), Myelofibrosis (n=3)	Mean Age: 46.56 (11.31) Gender: M = 50% F = 50% Race: White = 10 Black = 2 Latino = 2 Native American = 1 Asian = 1	Longitudinal; 4 assessments: pre-HCT, hospital discharge, 2 weeks post-discharge, 6 weeks post-discharge	EORTC QLQ-C30	One-way repeated measures ANOVA with paired samples t-tests and Bonferroni corrections	Sleep differences were found between T1 (M=41.67) and T2 (M=73.33) (baseline to immediately before discharge), & between T2 and T3 (M=33.33) (immediately before discharge to 2 weeks post-hospitalization). T4 M=33.33
Harder et al. (2002) (79)	HCT (N=40) Allo HCT (87.5%); Allo MRD=26, Allo	Age at HCT: Mean = 37.2	Cross-sectional; 22-82 months post-HCT	EORTC QLQ-C30	Descriptives	Sleep disruption M = 18.3 (SD=22.6)

Study	Sample	Demographics	Time Frame	Sleep Measures	Statistical Analyses	Main Relevant Findings
	MUD=9, Auto=5 ALL (n=8), AML (n=10), CML (n=6), NHL (n=6), MDS (n=4), MM (n=4), AA (n=2) All had TBI up to 12 Gy, Intrathecal tx (n=11), Conditioning Regimen: CY (n=12), ARA-C/CY (n=19), VP-16/CY (n=9)	Range = 15-55 Gender: M = 24 F = 16				Sleep disturbances were one of the most commonly reported complaints.
Hayden et al. (2004) (53)	Sibling Allo HCT (N=51) (original sample of 75 HCT patients) CY/TBI (32%); BU/CY (68%)	Based on 51 patients alive in 2003: Age at BMT: Median = 35 Range = 14-55 Gender: M = 31 F = 20	Cross-sectional; Median of 98 months post-HCT	EORTC QLQ-C30	Descriptives	No difference in sleep disruption between HCT patients and reference population. Reference population not described.
Hendriks & Schouten(2002) (45)	HCT (N=52 at T1; N=33 at T2) Auto (81%), Allo (19%) at T1 Relapse free Lymphoma (40%), Breast cancer (29%), Acute leukemia (29%)	Age: Mean = 41 Gender: M = 42% F = 58%	Longitudinal; Mean of 2.5 years & 4.5 years post-HCT	EORTC QLQ-C30	Mann-Whitney U test, correlations	No differences in sleep disruption over time. Patients reported more sleep disruption than general Norwegian population. Physicians tended to underestimate sleep problems.
Hjermstad et al. (2004) (33)	HCT (N=130), Chemotherapy patients (N=118) Allo (n=61), Auto (n=69) HCT Group: HD (n=15), high grade NHL (n=43), low grade NHL (n=11), CML (n=31), AML (n=19), ALL (n=11)	Age at baseline: Median = 35 Range = 17-55 Gender: M=56% F=44%	Longitudinal; Pre-HCT & 3-5 years post-HCT	EORTC QLQ-C30	Wilcoxon's test or one-way ANOVA as appropriate. Confidence intervals for graphic illustrations	No statistically significant changes in sleep disruption from baseline to 3-5 years in allo or auto groups, but CT group reported improved sleep quality over time. Allo patients reported better sleep, auto worse sleep than general Norwegian population at baseline and 3-5 years post- HCT.
Kiss et al. (2002) (57)	Allo HCT (N=28) Included both disease free & relapsed patients CML only CY/TBI/ARA-C (n=27), BU/CY (n=1)	Age: Mean = 32.6 Range = 18.2-49.2 Gender: M = 16 F = 12	Cross-sectional; Mean of 13.2 years post-HCT	Single item from a symptom checklist developed at the hospital	Descriptives	21 of 26 patients were mildly bothered by sleep disruption while 5 of 26 were moderately or severely bothered.
Kopp et al. (2005) (51)	HCT (N=34) & age- and sex-matched non-cancer controls (N=68) Allo HCT (61.8%), Auto HCT (38.2%) Chronic leukemia (14.7%), Acute leukemia (47.1%), MM (8.8%), MDS (5.9%), Solid tumor (2.9%), Lymphoma (17.6%), Sarcoma (2.9%) TBI fractionated (67.6%), TBI single dose (8.8%), No (23.5%)	Mean Age: 44.7 (9.4) Gender: M = 50% F = 50%	Cross-sectional; Patients were at least 5 years post-HCT	EORTC-QLQ C30	Mann-Whitney U-tests	No significant differences in sleep between HCT patients and healthy controls; patients had worse sleep by .06 SD.

Study	Sample	Demographics	Time Frame	Sleep Measures	Statistical Analyses	Main Relevant Findings
Messerer et al. (2008) (55)	Allo HCT (N=121) & Chemotherapy (N=221) Disease free AML Only	Allogeneic BMT: Age at diagnosis: Median = 38 Gender: F = 52%	Cross-sectional; HCT patients were a median of 8 years post-HCT; Chemo patients were a median of 9 years post-chemo	EORTC QLQ-C30	Chi-square, stratified Mantel-Haenszel, non parametrics	No difference in sleep disruption between allo HCT patients and chemotherapy patients (.06 SD).
Mosher et al. (2011) (56)	HCT (N=406) Auto (60.3%), Allo (29.1%) Relapse free NHL (22.4%), HD (6.2%), AML/CML (11.6%), ALL/ CLL (3.4%), MDS/MPS (8.4%), MM / Amyloidosis (33.7%), Other (1.5%)	Mean Age: 49.25 (12.82) Gender: M = 51.5% F = 47.8% Race: Caucasian = 83.7%, African American = 5.7%, Hispanic = 3.9%, West Indian = 1.5%, Other = 4.4%	Cross-sectional; Mean of 21 months post-HCT	FACT-BMT	Percentage	80% of patients reported sleeping well.
Pallua et al. (2010) (47)	Allo HCT (N=100) AML (41%), CML (22%), ALL (12%), Lymphoma (6%), MDS (6%), MM (4%), AA (4%), MPD (2%), PNH (2%), CLL (1%)	Age: Mean = 46.3 (14.7) Range = 16 – 76 Gender: M = 55% F = 45%	Cross-sectional; Mean of 95.4 months post-HCT	EORTC QLQ-C30	Effect Sizes = Cohen's d, t-tests, one way ANOVA	No significant association between sleep disruption and time since transplant. Sleep disruption was greater in patients with ongoing GVHD compared to patients with no GVHD (ES=.31; not significant). Difference in sleep disruption between HCT patients and the reference Austrian population (ES=.31).
Rischer et al. (2009) (4)	HCT (N=50 at pre-HCT, N=32 at Day 100 post-HCT) Allo (78%), Auto (22%) AML (36%), MM (22%), NHL (14%), MDS (10%), Osteomyelofribrosis (10%), Others (8%)	Mean Age: 53.3 (12.6) Gender: M = 74% F = 26%	Longitudinal; 3 assessments: Pre-HCT, During Hospital Stay, & Day 100 post-HCT	PSQI, Sleep Diary	Chi-square, McNemar tests, repeated measures ANOVA Spearman's correlation coefficients	Prevalence of sleep disruption 32% prior to HCT, 77% during hospitalization, 28% at day 100. During hospitalization: difficulties maintaining sleep was the most reported sleep dimension (81.8% moderate to severe, mainly caused by noises & toileting), then non-restorative sleep (61.4%), difficulties falling asleep (52.3%), difficulties falling back asleep (47.7%), & early a.m. awakenings (20.5%). Allo patients had significantly worse sleep than auto patients. Increases in sleep disruption correlated with increases in fatigue, physical functioning, treatment-specific distress but not anxiety and depression

Study	Sample	Demographics	Time Frame	Sleep Measures	Statistical Analyses	Main Relevant Findings
Sherman et al. (2003) (35)	Pre-BMT (N=61) MM (85.3%), MGUS (8.2%), Amyloid (6.6%)	Age: Mean = 57 (12.3) Gender: M = 63.9% F = 36.1% Race: White = 91.8% Other = 8.2%	Cross-sectional; Mean of 7.4 months post-diagnosis; All were assessed prior to BMT	Epworth Sleepiness Scale	Descriptives, Percentages, and Spearman Correlations	Pilot Study 43.33% exceeded the clinical cutoff of daytime sleepiness. Older age associated with more daytime sleepiness. Lower hemoglobin levels associated with more daytime sleepiness.
Syrjala et al. (2005) (52)	HCT survivors (N=137) & age- and sex-matched controls from the NHANES study (N=4020) Allo (88%), Auto (12%) CML (chronic phase) (45%), CML (accelerated or blast crisis) (7%), Acute leukemia in remission (14%), Acute leukemia in relapse (8%), Lymphoma in remission (10%), Lymphoma in relapse (7%), MDS (7%), Other (4%)	BMT survivors: Mean Age: 34.6 (9.0) Gender: M = 48% Race: White = 95% Non-white, Non-Hispanic = 3% Hispanic = 2%	Cross-sectional; 10 years post-HCT	Checklist of symptoms developed for the study	Paired *t*-tests, McNemar, Wilcoxon signed ranks tests Alphas set at .01.	14% of survivors reported moderate or severe sleep problems compared with 9% of controls; results were not statistically significant.
Watson et al. (2004) (59)	HCT (N=171) & chemotherapy (n=310) Allo (n=97), Auto (n=74) CY (n= 147), BU (n=26), mesna (n=27), MEL (n=18). TBI (n= 135)	For all groups: Age: Median = 39 Range = 15-58 Gender: M = 45% F = 55%	Cross-sectional; at least 1 year post-HCT	EORTC QLQ-C30	Wilcoxon two sample test, t-test, Generalized linear models	45% of patients reported sleep disruption. Sleep disruption more severe in older patients than younger patients. No difference in sleep disruption between allo, auto, or chemotherapy groups. No differences in sleep disruption between males and females.
Wettergren et al. (2008) (34)	Auto HCT (N=22), Compared to Swedish population norms HD (n=1), NHL (n=3), AML (n=6), MM (n=12)	Age: Median = 50 Range = 31 - 66 Gender: M = 13 F = 9	Longitudinal; Pre-HCT & 1 year post-HCT	EORTC QLQ-C30	McNemar test, paired t-test	No significant changes in sleep disruption (ES=. 03), no differences compared to Swedish population norms
Worel et al. (2002) (46)	Allo or syngeneic HCT (N=155) Disease-free ALL/AML (n=9/43), CML (n=56), MM (n=5), MDS (n=7), NHL (n=15), AA (n=19), Testicular cancer (n=1) TBI/CY, CY, CY/ATG, BU/CY	Age: Median = 34 Range = 17-57 Gender: M = 86 F = 69	Cross-sectional; at least 2 years post-HCT	EORTC QLQ-C30	Descriptives	Divided patients 2-5 years post-HCT & more than 5 years post- HCT. Of all patients, 45% had none or slight sleep disruption, 43% had moderate sleep disruption, and 12% had severe sleep disruption. Percentages were comparable for patients 2-5 years post-HCT and more than 5 years post-HCT.

AA: aplastic anemia; ALL: acute lymphoid leukemia; AML: acute myeloid leukemia; ARA-C: cytarabine; ATG: anti-thymocyte globulin; BEAM: carmustine, etoposide, cytarabine, melphalan; BU: busulfan; CLL: chronic lymphocytic leukemia; CY: cyclophosphamide; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core - 30; FACT-BMT: Functional Assessment of Cancer Therapy – Bone Marrow Transplant; FLU: fludarabine; HCT: hematopoietic cell transplant; HD: Hodgkin's disease; ISI: Insomnia Severity Index; MDASI: M.D. Anderson Symptom Inventory; MDS: myelodysplastic syndrome; MEL: melphalan; MGUS: monoclonal gammopathy of undetermined significance; MM: multiple myeloma; MOS: Medical Outcomes Study; MPS: myeloproliferative syndrome: MRD: matched related donor; MUD: matched unrelated donor; NHL: non-Hodgkin's lymphoma; PNH: paroxysmal nocturnal hemoglobinuria; PSQI: Pittsburgh Sleep Quality Index; RIC: reduced-intensity conditioning; SF-36: Medical Outcomes Study Short Form – 36; SIP: Sickness Impact Profile; TBI: total body irradiation; VP-16: etoposide; WHOQOL100: World Health Organization Quality of Life Questionnaire - 100

Table 2

Online Resources for Sleep Disorders and Disruption

Type of Intervention	Relevant Disorder(s)	Resource	Internet Address	Description	Evidence Base	Cost
Cognitive-behavioral interventions	Insomnia	SHUTi	www.shuti.me	• Interactive online program that includes videos from insomnia experts, interactive quizzes, and vignettes dealing with real-life sleep issues • Progress is tracked • Provides recommendations tailored to individuals' sleep difficulties	• Cancer patients • Adults	$129.00 For 16 weeks of access
	Insomnia	RESTORE	www.restorecbt.com	• Treatment consists of 5 modules with instructive videos and downloadable MP3 files	• Adults	Cost unspecified. Made available through patients health care provider. Also works with health insurance providers.
	Insomnia	Sleepio	www.sleepio.com	• Interactive online treatment is delivered by a virtual therapist and consists of 6 personally tailored interactive stages • Progress is tracked and each stage is adjusted accordingly	• Adults	Three payment plan options. $9.99 per week. $79.99 for 12 week access. $119.99 for 24 week access.
Education about insomnia and treatment	All sleep disorders	National Sleep foundation	www.sleepfoundation.org	• Comprehensive information about sleep, support groups, video and audio library, and sleep professional location assistance	N/A	Free
	All sleep disorders	Sleep Education	www.sleepeducation.com	• Comprehensive information about sleep difficulties, video archive, and sleep professional location assistance	N/A	Free

Type of Intervention	Relevant Disorder(s)	Resource	Internet Address	Description	Evidence Base	Cost
	All sleep disorders	Your Sleep	http://yoursleep.aasmnet.org	• Comprehensive information about sleep, self-administered sleep assessments, downloadable sleep diary, online forum, and sleep professional location assistance	N/A	Free
	Obstructive sleep apnea	American Sleep Apnea Association	http://sleepapnea.org/	• Self-administered screening for OSA, information about OSA, and information on support groups for people with OSA	N/A	Free
	Restless Leg Syndrome	Willis-Ekbom Disease Foundation	http://www.rls.org/	• Self-administered screening for RLS, information about RLS, and information on support groups for people with RLS	N/A	Free
Cancer-specific education about insomnia and treatment	Insomnia	National Cancer Institute	www.cancer.gov	• Information specific to cancer related sleep difficulties, symptom management tips, and modules • To find sleep information type “sleep” into the “search” box located on the upper right hand corner on the home page	N/A	Free
	General sleep health	American Cancer Society	www.cancer.org	• Information specific to cancer related sleep difficulties and treatment and symptom management tips • Available in Spanish. • To find sleep information type “sleep” into the “search” box located on the center on the home page	N/A	Free
	Insomnia	Cancer Support Community	www.cancersupportcommunity.org	• Information specific to cancer related sleep difficulties, tips for managing insomnia, hyper insomnia, and nightmares • To find sleep information type “sleep” into the “search” box located on the upper right hand corner on the home page	N/A	Free

Type of Intervention	Relevant Disorder(s)	Resource	Internet Address	Description	Evidence Base	Cost
Clinical trials search engines	All sleep disorders	National Cancer Institute	http://www.cancer.gov/clinicaltrials/search	• Search engine for nationwide cancer clinical trials • To find sleep-related clinical trials type “sleep” into the “keywords/phrases” box towards the middle of the page	N/A	Free
	All sleep disorders	National Institutes of Health	http://clinicaltrials.gov/	• Search engine for nationwide clinical trials • To find sleep-related clinical trials with cancer patients type “sleep AND cancer” into the “search for studies” box at the top of the page	N/A	Free

Table 3

Medications Recommended for Treatment of Insomnia by the American Academy of Sleep Medicine (16)

Drug Class	Agent(s)	FDA-approved for sleep onset (80)	FDA-approved for sleep maintenance (80)	Controlled substance	Generic Available	Relevant contraindications include (80)	RCT-demonstrated efficacy for insomnia up to	Relevant drug interactions
Short/Intermediate Acting Benzodiazepine Receptor Agonists	Eszopiclone (Lunesta)	Yes	Yes	Yes	Yes	Impaired motor/cognitive performance with higher dosage in elderly	6 months	CNS depressants, rifampicin, ketoconazole
	Temazepam (Restoril)	Yes	Yes	Yes	Yes	Oversedation, confusion, ataxia with higher dosage in elderly	8 weeks	CNS depressants, hypnotics, diphenhydramine
	Triazolam (Halcion)	Yes	No	Yes	Yes	Compromised respiratory function, renal or hepatic impairment, pulmonary insufficiency	5 weeks	Ketoconazole, itraconazole, nefazodone, HIV protease inhibitors, medications that impair the oxidative metabolism mediated by CYP3A
	Zaleplon (Sonata)	Yes	No	Yes	Yes	Conditions affecting metabolism or hemodynamic responses or compromised respiratory function	4 weeks	Promethazine; rifampin; CYP3A4 inducers; CYP3A4 inhibitors; cimetidine; additive CNS depression with other psychotropic medications, anticonvulsants, antihistamines, narcotic analgesics, anesthetics, ethanol, and other CNS depressants
	Zolpidem (Ambien)	Yes	No	Yes	Yes	Compromised respiratory function, conditions affecting metabolism or hemodynamic responses, renal or hepatic impairment, risk of impaired motor/cognitive performance in elderly	8 months	CNS depressants; other sedative-hypnotics; imipramine; chlorpromazine; alcohol; sertraline; CYP3A4 inhibitors; rifampin; fluoxetine; ketoconazole
	Zolpidem (Ambien CR)	Yes	Yes	Yes	Yes	Compromised respiratory function, conditions affecting	6 months	CNS depressants; other sedative-hypnotics;

Drug Class	Agent(s)	FDA-approved for sleep onset (80)	FDA-approved for sleep maintenance (80)	Controlled substance	Generic Available	Relevant contraindications include (80)	RCT-demonstrated efficacy for insomnia up to	Relevant drug interactions
						metabolism or hemodynamic responses, renal or hepatic impairment, risk of impaired motor/cognitive performance in elderly		imipramine; chlorpromazine; alcohol; sertraline; CYP3A4 inhibitors; rifampin; fluoxetine; ketoconazole
	Zolpidem (Intermezzo)	No	Yes	Yes	No	Compromised respiratory function, risk of impaired motor/cognitive performance in elderly	4 weeks	CNS depressants; imipramine; chlorpromazine; rifampin; ketoconazole
Melatonin Receptor Agonist	Ramelteon (Rozerem)	Yes	No	No	Yes	Hepatic impairment, may affect reproductive hormones	6 months	CYP inducers, CYP1A2 inhibitors, CYP3A4 inhibitors, CYP2C9 inhibitors; donepezil; doxepin; zolpidem; CNS depressants; alcohol
Intermediate/Long Acting Benzodiazepine Receptor Agonist	Clonazepam (Klonopin)	No	No	Yes	Yes	Renal or hepatic impairment, respiratory diseases, elderly patients, glaucoma	None	CYP450 inducers; propantheline; CYP3A inhibitors; alcohol; narcotics; barbiturates; hypnotics; antianxiety agents; phenothiazines; thioxanthene; butyrophenone antipsychotics; MAOIs; TCAs; anticonvulsant drugs; CNS depressants; valproic acid
	Estazolam (ProSom, Eurodin)	Yes	No	Yes	Yes	Renal or hepatic impairment, compromised respiratory function, depression	1 week	CNS-acting drugs; anticonvulsants; antihistamines; alcohol; barbiturates; MAOIs; narcotics; phenothiazines; psychotropic medications; CNS depressants; smoking; CYP3A inhibitors; CYP3A inducers
	Flurazepam (Dalmane)	Yes	Yes	Yes	Yes	Depression, hepatic or renal impairment,	3 weeks	CNS depressants; alcohol

Drug Class	Agent(s)	FDA-approved for sleep onset (80)	FDA-approved for sleep maintenance (80)	Controlled substance	Generic Available	Relevant contraindications include (80)	RCT-demonstrated efficacy for insomnia up to	Relevant drug interactions
						pulmonary insufficiency		
	Lorazepam (Ativan)	No	No	Yes	Yes	Compromised respiratory function, impaired renal or hepatic function, elderly	None	CNS depressants; clozapine; valproate; probenecid; theophylline; aminophylline
Sedating low-dose antidepressant	Amitriptyline	No	No	No	Yes	Liver dysfunction	None	Guanethidine; CNS depressants; CYP2D6 inhibitors; TCAs; SSRIs; “caution with thyroid drugs”; disulfiram; ethchlorvynol; anticholinergics; sympathomimetics; neuroleptics; cimetidine
	Doxepin (Silenor) 3-6mg	No	Yes	No	Yes	Compromised respiratory function	12 weeks	Alcohol; CNS depressants; sedating antihistamines; CYP2C19 inhibitors; CYP2D6 inhibitors; CYP1A2 inhibitors; CYP2C9 inhibitors; cimetidine; tolazamide; sertraline

Drug Class	Agent(s)	FDA-approved for sleep onset (80)	FDA-approved for sleep maintenance (80)	Controlled substance	Generic Available	Relevant contraindications include (80)	RCT-demonstrated efficacy for insomnia up to	Relevant drug interactions
	Mirtazapine (Remeron)	No	No	No	Yes	Neutropenia and hyponatremia reported, renal or hepatic impairment, conditions affecting metabolism or hemodynamic responses, elderly, may cause orthostatic hypotension	None	MAOIs; serotonergic drugs; drugs affecting hepatic metabolism; CYP enzyme inducers; drugs metabolized by or inducers of cytochrome P450; antihypertensives known to cause hyponatremia; phenytoin; carbamazepine; hepatic metabolism inducers; cimetidine; ketoconazole; cimetidine; alcohol; diazepam; CYP3A4 inhibitors; HIV protease inhibitors; azole antifungals; erythromycin; nefazodone; warfarin
	Trazodone (Oleptro)	No	No	No	Yes	Hypotension and syncope reported, elderly, renal or hepatic impairment, hyponatremia may occur	1 week	Serotonergic drugs; drugs which impair serotonin metabolism; antipsychotics; dopamine agonists; serotonin precursors; CYP3A4 inhibitors; Carbamazepine; MAOIs; alcohol; barbiturates; CNS depressants; warfarin; antihypertensives; NSAIDs; aspirin; drugs that affect coagulation or bleeding; diuretics; drugs that prolong QT interval
	Trimipramine (Surmontil)	No	No	No	Yes	Liver dysfunction, elderly	None	Serotonergic drugs; drugs which impair serotonin metabolism; caution on patients on thyroid medication; guanethidine;

Drug Class	Agent(s)	FDA-approved for sleep onset (80)	FDA-approved for sleep maintenance (80)	Controlled substance	Generic Available	Relevant contraindications include (80)	RCT-demonstrated efficacy for insomnia up to	Relevant drug interactions
								cimetidine; alcohol; catecholamines; anticholinergics; sympathomimetic amines; local decongestants; local anesthetics containing epinephrine; atropine; CYP2D6 inhibitors; SSRIs; TCAs
Other prescription drugs	Gabapentin (Neurontin)	No	No	No	Yes	Liver dysfunction, hepatic impairment	None	Maalox; naproxen sodium; hydrocodone
	Olanzapine (Zyprexa)	No	No	No	Yes	Hepatic impairment; prostatic hypertrophy; may cause orthostatic hypotension; leukopenia, neutropenia, and agranulocytosis reported; may cause cognitive and motor impairment	None	Diazepam; alcohol; carbamazepine; omeprazole; rifampin; CYP1A2 inducers; fluoxetine; fluvoxamine; other centrally-acting drugs; potentially hepatotoxic drugs; antihypertensives; levodopa; dopamine agonists; anticholinergic drugs; parenteral benzodiazepines
	Tiagabine (Gabitril)	No	No	No	Yes	Tiagabine (Gabitril) No No No Yes Incapacitating weakness reported	1 night	valproate; carbamazepine; phenytoin; phenobarbital; ethanol; triazolam; drugs that lower seizure threshold (antidepressants, antipsychotics, stimulants, narcotics); drugs that induce or inhibit hepatic metabolizing enzymes; highly protein-bound drugs
	Quetiapine (Seroquel)	No	No	No	Yes	May induce orthostatic hypotension; leukopenia, neutropenia, and agranulocytosis reported; may impair	None	Centrally-acting drugs; alcohol; CYP3A4 inhibitors; CYP3A4 inducers; antihypertensives;

Drug Class	Agent(s)	FDA-approved for sleep onset (80)	FDA-approved for sleep maintenance (80)	Controlled substance	Generic Available	Relevant contraindications include (80)	RCT-demonstrated efficacy for insomnia up to	Relevant drug interactions
						physical/mental abilities		levodopa; dopamine agonists; drugs known to cause electrolye imbalance; drugs known to prolong QTc interval (e.g., antiarrhythmics, antipsychotics, antibiotics); anticholinergic medications