

Original Article

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Author for correspondence:

Melanie T. Gentry M.D., Department of Psychiatry and Psychology, Mayo Clinic Rochester, 200 1st Street SW, Rochester, MN 55905. E-mail: gentry.melanie@mayo.edu

Effects of a multidisciplinary quality of life intervention on sleep quality in patients with advanced cancer receiving radiation therapy

Melanie T. Gentry, M.D.¹ , Pamela J. Atherton, M.S.², Maria Lapid, M.D.¹, Preetha Sharone Rosen, M.D.³, Simon Kung, M.D.¹, Jarrett Richardson, M.D.¹, Shehzad K. Niazi, M.D.⁴, William V. Bobo, M.D.⁴, Matthew M. Clark, P.H.D.¹ and Teresa A. Rummans, M.D.^{1,4}

¹Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN; ²Cancer Center Statistics Section, Division of Biomedical Statistics and Informatics, Department of Health Sciences, Mayo Clinic, Rochester, MN; ³Peace Health St John Medical Center, Longview, Washington, WA and ⁴Department of Psychiatry and Psychology, Mayo Clinic, Jacksonville, FL

Abstract

Objectives. Sleep disturbances are prevalent in cancer patients, especially those with advanced disease. There are few published intervention studies that address sleep issues in advanced cancer patients during the course of treatment. This study assesses the impact of a multidisciplinary quality of life (QOL) intervention on subjective sleep difficulties in patients with advanced cancer.

Method. This randomized trial investigated the comparative effects of a multidisciplinary QOL intervention ($n = 54$) vs. standard care ($n = 63$) on sleep quality in patients with advanced cancer receiving radiation therapy as a secondary endpoint. The intervention group attended six intervention sessions, while the standard care group received informational material only. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS), administered at baseline and weeks 4 (post-intervention), 27, and 52.

Results. The intervention group had a statistically significant improvement in the PSQI total score and two components of sleep quality and daytime dysfunction than the control group at week 4. At week 27, although both groups showed improvements in sleep measures from baseline, there were no statistically significant differences between groups in any of the PSQI total and component scores, or ESS. At week 52, the intervention group used less sleep medication than control patients compared to baseline ($p = 0.04$) and had a lower ESS score (7.6 vs. 9.3, $p = 0.03$).

Significance of results. A multidisciplinary intervention to improve QOL can also improve sleep quality of advanced cancer patients undergoing radiation therapy. Those patients who completed the intervention also reported the use of less sleep medication.

Introduction

Patients with cancer commonly experience sleep problems, with 24–95% of cancer patients reporting some type of sleep difficulty (Clark *et al.*, 2004; Page *et al.*, 2006; Delgado-Guay *et al.*, 2011; Nishiura *et al.*, 2015). Advanced cancer patients in palliative care show even more difficulty with sleep. In one study of 219 advanced cancer patients, all patients reported significant sleep difficulty, and sleep problems were highly correlated with psychological distress (Mercadante *et al.*, 2017). Many types of subjective sleep symptoms are reported by cancer patients, including difficulty initiating and maintaining sleep, early morning awakenings, nonrestorative sleep, and excessive daytime sleepiness (Beszterczey and Lipowski, 1977; Owen *et al.*, 1999; Davidson *et al.*, 2002; Clark *et al.*, 2004). Studies using objective measures, such as actigraphy and polysomnography, also indicate high levels of sleep difficulties in cancer patients, including circadian rhythm dysfunction (Mormont and Waterhouse, 2002), poor sleep quality (Parker *et al.*, 2008; Garrett *et al.*, 2011; Grutsch *et al.*, 2011), decreased sleep efficiency (Garrett *et al.*, 2011; Palesh *et al.*, 2014), and increased nighttime awakenings (Dhruva *et al.*, 2012). Several factors are associated with sleep disturbances, including demographic (older age, female, and Caucasian), psychosocial (stress, social support, and mental illness), and disease or treatment related factors (pain, medications, radiation, and chemotherapy), thereby implying a multifactorial etiology (Berger *et al.*, 2005) of sleep difficulties in patients with advanced cancer.

While sleep difficulties are highly prevalent in patients with advanced cancer, most of the intervention studies to improve sleep in cancer populations have been in early stage cancer

patients. There are few psychosocial or pharmacological intervention studies to address sleep issues in patients with advanced cancer or receiving active cancer treatment (Mystakidou *et al.*, 2009). This is an important gap in the current knowledge base given the results of numerous studies that have shown a worsening of sleep disturbances during cancer treatment in general, and during radiation therapy, in particular (Hickok *et al.*, 2005; Palesh *et al.*, 2010; Miaskowski *et al.*, 2011). Several types of interventions have been investigated to improve sleep and reduce fatigue in cancer patients. A 2014 systematic review identified 12 studies using Cognitive Behavioral Therapy for Insomnia (CBT-I) to treat insomnia in cancer patients. The reviewers found that CBT-I is associated with significant improvements in subjective sleep measures and that it may also improve the overall quality of life (QOL) (Garland *et al.*, 2014b). However, adherence to CBT-I treatment can be problematic even in healthy adults (Matthews *et al.*, 2014). Some aspects of CBT-I may be particularly difficult for cancer patients in active treatment, such as sleep restriction. In addition, cancer patients may not always recognize the role of chronic insomnia in their overall health and may not be as motivated to participate in insomnia focused treatment. More general interventions such as Mindfulness Based Cancer Recovery, an adaptation of Mindfulness Based Stress Reduction (MBSR) have been shown to be equally effective to CBT-I in improving sleep in cancer patients (Garland *et al.*, 2014a). Interventions that target multiple domains of QOL and sleep have a potential for increased acceptance amongst cancer patients and a potential to have more wide reaching areas for improvement. We thus investigated the secondary endpoint of sleep quality in 117 advanced cancer patients who were receiving radiation therapy and who participated in a multidisciplinary intervention targeting domains of QOL (physical, mental, emotional, social, and spiritual). The primary aim of the original study, described elsewhere (Clark *et al.*, 2013), focused on intervention effects on overall QOL. This secondary analysis compares the effects of the multidisciplinary QOL intervention vs. standard care. This intervention incorporated support from an adult caregiver for all participants. Particularly in patients with advanced cancer and in active treatments, caregivers play a vital role in the overall QOL of patients. Several studies have demonstrated treatment benefits from involving caregivers in the psychosocial intervention (Mishel *et al.*, 2002; Nezu *et al.*, 2003).

Methods

Study design

This was a Mayo Clinic Institutional Review Board-approved clinical trial conducted at the Mayo Clinic Cancer Center. Eligibility criteria included having an initial diagnosis of cancer within 12 months prior to study entry, intermediate to poor prognosis (0–50% expected 5-year survival), and an Eastern Cooperative Oncology Group performance status of 0 (fully active), 1 (able to perform light work), or 2 (ambulatory and capable of self-care but unable to do any type of work). Participants were required to have caregivers willing to participate. Patients with cognitive impairment (a Mini-Mental State Examination score <20), expected survival of <6 months, active substance abuse (alcohol or drugs), participation in other psychosocial trials, active untreated thought disorder, suicide risk, or requiring psychiatric hospitalization were excluded. Patients were randomly assigned via a Pocock-Simon dynamic allocation procedure, which

assigned patients to the arm that minimized the stratification factor imbalance with 75% probability (Pocock and Simon, 1975) to the intervention group or a standard care group.

The intervention consisted of six structured sessions, each of 90 min duration beginning with conditioning exercises (physical domain of QOL), followed by education, CBT strategies for coping with cancer (mental and emotional domains of QOL), open discussion and support (social QOL), discussion of a spiritual topic with a chaplain (spiritual QOL), and a 15 min deep breathing or guided imagery relaxation exercise (emotional QOL). Caregivers were invited to attend sessions 1, 3, 4, and 6. The intervention focused on the patient, with caregivers providing support to the patient. A clinical psychologist or psychiatrist led all multidisciplinary sessions, with involvement from other staff members based on session content areas. Other staff members included an advanced practice nurse, a certified hospital chaplain, a licensed physical therapist, and a licensed independent clinical social worker. One session involved sleep hygiene education including the following strategies: having a consistent bedtime routine, not watching the clock, and using the bed only for sleeping. The details of the other sessions are documented in detail elsewhere (Clark *et al.*, 2013). Participants received 10 brief structured telephone counseling sessions over the 6 months following the intervention. Telephone contact was used to promote long-term maintenance of health behavior change. There was no long-term effect found for the telephone contact in the original analysis. Standard care consisted of ongoing medical care and written informational material only. Written information consisted of a large library of patient educational materials. The use of this material by participants was not monitored.

Measures

The study measures were administered at baseline and weeks 4 (post-intervention), 27, and 52. Measures used to assess sleep difficulties were the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS). The PSQI measures the quality of sleep and provides a total score (range 0–21) and 7 component scores (each ranging from 0 to 3: sleep quality, latency, duration, efficiency, disturbance, medication, and daytime dysfunction), where lower scores indicate less difficulty (Buysse *et al.*, 1989). A score ≥ 5 on the PSQI is generally indicative of a “poor” sleeper and suggests a subjective sleep disorder (Buysse *et al.*, 1989). The ESS assesses daytime sleepiness using 8 situations in which patients rate on a scale from 0 to 3 where 0 = “no chance of dozing” and 3 = “high chance of dozing.” A total score is calculated using the individual scales with a range of 0–24, with lower scores indicating less chance of dozing (Johns, 1991).

The other self-reported measures included in this study were related to QOL and mood states. The Linear Analogue Self-Assessment is a series of QOL-related items, which has been validated in cancer patients. Items include overall QOL, mental well-being (WB), physical WB, emotional WB, social activity, and spiritual WB (Bretschler *et al.*, 1999; Locke *et al.*, 2007; Sloan *et al.*, 2012). Each item is measured on an 11-point Likert scale, ranging from 0 = “As bad as it can be” to 10 = “As good as it can be.” The Functional Assessment of Cancer Therapy – General is a 28 item assessment for cancer patients with any tumor type (Cella *et al.*, 1993). Questions are scored from 0 = “Not at all” to 4 = “Very much” and are compiled into four subscales: functional, physical, social/family, and emotional WB.

Table 1. Baseline patient characteristics

	Intervention (N = 54)	Control (N = 63)	Total (N = 117)	p Value
Age				0.6477 ^a
Mean (SD)	59.2 (10.9)	60.3 (11.2)	59.8 (11.0)	
Median	60.0	61.0	60.0	
Age Group				0.7220 ^b
<50	9 (16.7%)	9 (14.3%)	18 (15.4%)	
50+	45 (83.3%)	54 (85.7%)	99 (84.6%)	
Gender				0.6940 ^b
Female	19 (35.2%)	20 (31.7%)	39 (33.3%)	
Male	35 (64.8%)	43 (68.3%)	78 (66.7%)	
Race				0.2563 ^b
White	52 (96.3%)	61 (96.8%)	113 (96.6%)	
Other	2(3.8%)	2 (3.2%)	4 (3.5%)	
Dominant disease status				0.4051 ^b
Brain	8 (14.8%)	17 (27.0%)	25 (21.4%)	
Head and neck	7 (13.0%)	10 (15.9%)	17 (14.5%)	
Lung	10 (18.5%)	7 (11.1%)	17 (14.5%)	
GI	21 (38.9%)	23 (36.5%)	44 (37.6%)	
Other	8 (14.8%)	6 (9.5%)	14 (12.0%)	
Tumor grade				0.1202 ^b
1–2	9 (16.7%)	4 (6.3%)	13 (11.1%)	
3	20 (37.0%)	30 (47.6%)	50 (42.7%)	
4	13 (24.1%)	22 (34.9%)	35 (29.9%)	
5	12 (22.2%)	7 (11.1%)	19 (16.2%)	
Performance score				0.8186 ^b
Fully active	30 (55.6%)	32 (50.8%)	62 (53.0%)	
Restricted	23 (42.6%)	29 (46.0%)	52 (44.4%)	
Ambulatory	1 (1.9%)	2 (3.2%)	3 (2.6%)	
Planned treatment				0.6168 ^b
Radiation	9 (16.7%)	9 (14.3%)	18 (15.4%)	
Chemotherapy	0 (0.0%)	1 (1.6%)	1 (0.9%)	
Both	45 (83.3%)	53 (84.1%)	98 (83.8%)	
Education level				0.2448 ^b
H.S. graduate/GED or less	15 (27.8%)	11 (17.4%)	26 (22.2%)	
Some college or vocational	16 (29.6%)	21 (33.3%)	37 (31.6%)	
Graduate w/ 4 yr degree	12 (22.2%)	11 (17.5%)	23 (19.7%)	
Some post graduate study or more	9 (16.7%)	13 (20.1%)	22 (18.8%)	
Other	2 (3.7%)	7 (11.1%)	9 (7.7%)	
Work while undergoing treatment				0.9120 ^b
Yes	11 (35.5%)	13 (34.2%)	24 (34.8%)	
Marital status				0.0868 ^b
Married	48 (88.9%)	52 (82.5%)	100 (85.5%)	
Separated/divorced/single	1 (1.9%)	9 (14.2%)	10 (8.5%)	

(Continued)

Table 1. (Continued)

	Intervention (N = 54)	Control (N = 63)	Total (N = 117)	p Value
Widowed	5 (9.3%)	2 (3.2%)	7 (6.0%)	
Meditation use				0.1324 ^b
Yes	46 (85.2%)	59 (93.7%)	105 (89.7%)	
Religious affiliation				0.1207 ^b
Catholic	14 (25.9%)	28 (44.4%)	42 (35.9%)	
Protestant	32 (59.3%)	32 (50.8%)	64 (54.7%)	
Jewish	2 (3.7%)	0 (0.0%)	2 (1.7%)	
None	5 (9.3%)	2 (3.2%)	7 (6.0%)	
Other	1 (1.9%)	1 (1.6%)	2 (1.7%)	

^aKruskal Wallis.^bChi-Square.**Table 2.** ESS results

Week	Intervention	Control	p Value*
0	7.3	8.2	0.21
4	7.6	8.7	0.14
27	7.5	8.4	0.15
52	7.6	9.3	0.03

Range 0–24 where 0 is no chance of dozing and 24 is high chance of dozing.

*Significant at $p \leq 0.05$

Analysis

Assessments were scored according to their specific scoring algorithms. Changes from baseline were calculated. Patients were categorized as having increases or decreases in the various scores and categorized as having PSQI-defined sleep improvement or no sleep improvement. PSQI-defined sleep improvement was defined as a score of less than or equal to 5. Conversely, sleep problems were defined as a PSQI score greater than 5. Comparisons were made between intervention and control patients using the Chi-square or Fischer's exact test for ordinal data and Wilcoxon methodology for continuous data. Repeated measures ANOVA modeling were performed to determine whether relationships over time, if any, existed between the patient's sleep performance and other baseline QOL scores or patient characteristics.

Hypothesis testing used a two-tailed alternative and a 5% Type I error rate. The primary analysis of the parent study was ensured to have 80% power to detect a clinically significant difference of 0.5 standard deviations (a shift of 8% or more on a 100-point scale) in QOL scores between study arms. The statistical analyses presented here are exploratory and hypothesis generating without adjustment for multiple testing due to limited sample size.

Results

Patients in the intervention group were evaluable for the primary endpoint if they completed both baseline and week 4 assessments and participated in at least 4 of 6 intervention sessions. There were 117 evaluable patients (54 in the intervention group and 63 in the standard care group). Patients had a median age of

60 ± 11 years at baseline and were predominantly male (67%). Cancer types included gastrointestinal (GI) (38%), brain (21.4%), head and neck (14.5%), lung (14.5%), and other (12.0%) cancers (Table 1). The majority had radiation and chemotherapy (84%) and had a history of prior cancer surgery (96%). There were no significant differences on ESS scores between groups at baseline, week 4, or week 27 (see Table 2). An individual ESS item analysis showed that the intervention group reported a lower chance of dozing at week 52 (7.6 vs. 9.3, $p = 0.03$).

At baseline, there were no differences between study arms for sleep difficulties as measured by the PSQI score (see Table 3). At baseline, PSQI-defined sleep problems were found in 62.4% of all patients enrolled. In our sample, sleep problems existed in a total of 73 patients (37 intervention and 36 standard care) ($p = 0.36$). Characteristics of those with sleep problems were similar between groups, with sleep problems being associated with older age (age > 50) and male gender; older (87%), male (65%) for the intervention group; and older (89%), male (56%) for the standard care group.

For measures of sleep quality, at week 4, the intervention group showed a better PSQI total score change from baseline than the control group (−0.7 vs. 0.3, $p = 0.04$). Two of the seven domains also improved from baseline: sleep quality (−0.2 vs. 0, $p = 0.04$) and daytime dysfunction (−0.1 vs. 0.3, $p < 0.01$) (Table 2). The intervention group also had PSQI scores indicating less daytime dysfunction (0.9 vs. 1.3, $p = 0.01$). While not statistically significant compared to control, the intervention group showed improvements in sleep latency and duration and used less sleep medication. In the intervention group ($n = 47$), 21 (45%) patients had improvement in both PSQI and overall QOL, 25 (53%) had improvement in PSQI and emotional WB, 21 (45%) had improvement in PSQI and social activity, and 23 (49%) had improvement in PSQI and spiritual WB (QOL data not shown).

At week 27, the intervention group showed greater improvement over standard care in all PSQI component changes from baseline except daytime dysfunction (0.7 vs. 1.3). However, none of these improvements were statistically significant (data not shown). In the intervention group ($n = 43$), 25 (58%) patients had improvement in both PSQI and overall QOL, and 27 (63%) had improvement in PSQI and emotional WB (Analysis for intervention group only, no p value calculated).

Table 3. PSQI results (mean (SD))

	Week 0			Week 4		
	Intervention (N = 54)	Control (N = 63)	p value	Intervention (N = 54)	Control (N = 63)	p value
Sleep quality	1.1 (0.7)	1.0 (0.7)	0.25	0.9 (0.6)	1.0 (0.8)	0.67
Sleep quality change				-0.2 (0.6)	0.0 (0.7)	0.04
Sleep latency	1.2 (1.0)	0.9 (0.8)	0.08	1.1 (0.8)	0.9 (0.9)	0.11
Sleep latency change				-0.2 (0.9)	0.0 (0.8)	0.44
Sleep duration	0.4 (0.7)	0.4 (0.8)	0.91	0.3 (0.6)	0.4 (0.8)	0.77
Sleep duration change				-0.1 (0.5)	0.0 (0.9)	0.59
Sleep efficiency	0.8 (1.0)	0.7 (1.0)	0.42	0.7 (1.0)	0.6 (0.9)	0.74
Sleep efficiency change				0.0 (1.1)	-0.1 (1.0)	0.86
Sleep disturbance	1.6 (0.6)	1.6 (0.5)	0.74	1.6 (0.6)	1.6 (0.6)	0.50
Sleep disturbance change				0.0 (0.5)	-0.1 (0.7)	0.30
Sleep medication	1.1 (1.4)	0.9 (1.2)	0.49	0.9 (1.4)	1.1 (1.3)	0.52
Sleep medication change				-0.2 (1.2)	0.1 (1.1)	0.13
Daytime dysfunction	1.0 (0.7)	0.9 (0.6)	0.63	0.9 (0.6)	1.3 (0.8)	0.01
Daytime dysfunction change				-0.1 (0.7)	0.3 (0.8)	<0.01
PSQI total	7.3 (3.5)	6.4 (3.1)	0.15	6.5 (3.2)	6.6 (3.4)	0.94
PSQI total change				-0.7 (2.7)	0.3 (2.8)	0.04

Component score range 0–3 where 0 = no difficulty and 3 = severe difficulties. Total score range 0–21 where 0 = no difficulty and 21 = severe difficulties. Negative change scores indicate an improvement from baseline.

*Significant at $p \leq 0.05$.

At week 52, there were no statistically significant differences between groups in PSQI changes from baseline. However, intervention patients reported using less sleep medication (0.6 vs. 1.1, $p = 0.04$). This is a decrease of 0.5 points from baseline for intervention patients and an increase of 0.2 points for standard care patients. Sleep medication scores measure the number of times per week patients uses sleep medication (0 = none, 1 = less than once per week, 2 = once or twice a week). Of the 36 patients still participating in the intervention group, 21 (58%) patients had increases in both PSQI and overall QOL (Analysis for intervention group only, no p value calculated).

Repeated measure results indicated neither sex nor employment status was significant independent factors for modeling the PSQI score, but age group ($p = 0.03$) and baseline overall QOL ($p < 0.001$) were. The model using the ESS score as the dependent variable resulted in no significant independent factors.

Discussion

In this secondary analysis of a randomized controlled trial of a multidisciplinary structured intervention targeting multiple QOL domains, participants with advanced cancer who received the intervention demonstrated an improvement in sleep. This improvement was statistically significant only at week 4 (post-intervention). The only statistically significant outcome at longer term follow-up was that the intervention group patients used less sleep medication and were less sleepy than the control group at week 52.

An association between sleep and QOL has been shown in several studies in both the general population (Reimer and Flemons,

2003; Sateia and Pigeon, 2004) and in cancer patients (Clark et al., 2004; Vena et al., 2006; Mystakidou et al., 2007b). In one study, poor QOL was one of the strongest predictors of poor sleep quality in advanced cancer patients referred for palliative care (Mystakidou et al., 2009). Sleep issues have been associated with increased pain, depression, fatigue, decreased immune function, and increased mortality (Sephton and Spiegel, 2003; Stepanski et al., 2009; Delgado-Guay et al., 2011; Lehrer et al., 2013). One study showed that better sleep efficiency as measured by actigraphy predicted a significant reduction in mortality in advanced breast cancer patients even after adjusting for other prognostic factors (Palesh et al., 2014). Poor sleep has also been shown to hasten the desire for death in cancer patients (Mystakidou et al., 2007a). Our sample supports previous findings that rates of sleep disturbance in advanced cancer patients are very high. Other studies have shown rates of sleep dysfunction in advanced cancer patients ranging from 47% to 100% (Gibbins et al., 2009; Mystakidou et al., 2009; Yennurajalingam et al., 2015; Mercadante et al., 2017). In our sample of advanced cancer patients, 62.4% reported sleep difficulties. The intervention group reported significant improvements in sleep quality and reduced daytime dysfunction compared to the control group at week 4. However, these improvements were no longer statistically significant at follow-up. At week 52, the intervention group used less sleep medication and reported significantly less daytime sleepiness.

Many of the psychosocial intervention studies in cancer patients have focused on cognitive behavioral therapy alone (Clark et al., 2004; Dalton et al., 2004; Berger et al., 2005; Page et al., 2006; Berger, 2009). Our intervention is unique in that it

is a multidisciplinary approach which addressed multiple domains of QOL, including physical, emotional, cognitive, social, and spiritual. This intervention also allowed patients' caregivers to participate. In a post-session survey, the majority of the patients reported that coping strategies, relaxation techniques, and education were very helpful. Although this QOL intervention was not designed with the primary goal of improving sleep, positive benefits on sleep have been reported using a variety of psychosocial approaches and exercise techniques similar to those provided in this intervention. A randomized controlled trial on stage IV lung and colorectal cancer patients showed that home-based exercise program improved sleep quality (Cheville et al., 2013). Savard et al. (2006) showed that cognitive therapy improved both depression and insomnia in women with metastatic breast cancer. MBSR improved sleep quality in a study sample of 63 cancer patients with different types and stages of cancer (Carlson and Garland, 2005). Expressive writing was helpful with sleep disturbances in patients with metastatic renal cell carcinoma compared to neutral writing (de Moor et al., 2002). In a study by Cohen et al. (2004), Tibetan yoga improved sleep outcomes in lymphoma patients in various stages of the disease. A 2012 pilot study examined a patient-controlled cognitive behavioral intervention to improve pain, fatigue, and sleep in advanced cancer patients (Kwekkeboom et al., 2012). While the intervention improved the symptoms cluster as whole, the intervention did not result in improvements in sleep quality.

Our study has some limitations. The demographics of our participants from the cancer center who were generally Caucasian from the Midwest may not apply to a more diverse population. This secondary analysis examined the changes in sleep quality from an intervention primarily designed to improve overall QOL. Sleep quality was assessed using self-report measures rather than objective sleep studies. Despite these limitations, our results provide evidence that multidisciplinary QOL interventions can contribute to sleep improvement in advanced cancer patients.

In summary, we found that our multidisciplinary intervention to improve QOL for advanced cancer patients receiving radiation treatment also improved some components of sleep at post-intervention, as well as a few at longer term follow-up. Many psychosocial interventions have shown to be beneficial for improving sleep in cancer patients but few have addressed both sleep and QOL. This multidisciplinary intervention also included caregivers, who may also experience sleep disturbance. Additional studies are needed to examine the potential benefits of such an intervention for improving cancer caregiver sleep quality. As QOL and sleep disturbance appear to have a bidirectional association, interventions that target both QOL and sleep needs are likely to be beneficial in the treatment of cancer patients. Given the multifactorial etiology of sleep disturbances and the profound need for sleep intervention studies in advanced cancer patients, future clinical trials should incorporate multidisciplinary interventions to address QOL, sleep quality, and their impact on long-term survival.

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