Title: Effectiveness of aerobic exercise and mind-body exercise in cancer patients with poor sleep quality: A systematic review and meta-analysis of randomized controlled trials

Running title: Aerobic and Mind-body exercises in cancer patients with poor sleep

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Summary: Exercise has promising effects on sleep disturbances and quality of life among cancer patients. Aerobic exercise (AE) and mind-body exercises (MBE) have different mechanisms for improving sleep, but whether they are effective remains unclear. This systematic review and meta-analysis is the first to examine the effectiveness of AE and MBE on sleep outcomes, specifically among cancer patients with sleep disturbances. A systematic search of several databases, from inception to January 2018, was conducted. The pooled effect sizes suggested that both AE (SMD=0.33, 95% CI: 0.11, 0.54) and MBE (SMD=0.18, 95% CI: 0.06, 0.30), improved sleep outcomes in cancer patients with poor sleep quality post-intervention. The effects remained significant after 3-6 months for AE, but not MBE. Due to the heterogeneity in AE, future studies should establish the optimal AE prescription. For MBE, future research should study essential components that make the intervention effect sustainable.

Keywords: aerobic exercises, mind-body exercises, poor sleep, cancer patients

Glossary of terms: N/A

Abbreviations: AE, aerobic exercises; GSDS, General Sleep Disturbance Scale; MBE, mind-body exercises; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PSQI, Pittsburgh Sleep Quality Index; RCT, randomized controlled trials; SMD, standardized mean difference.

Introduction

Rationale

Cancer patients often experience symptoms that may persist for years; sleep disturbance is common. The prevalence of sleep disturbance in cancer ranges from 23-87% [1-3], of which up to 67% is clinical insomnia [4, 5]. Sleep disturbance occurs throughout the course of the disease [1, 6], increasing gradually from the treatment [7] to the post-treatment phase [8]. It reduces quality of life [4]. Cancer patients with sleep disturbance struggle to cope with stress and the activities of daily living [9], and they report more pain, less energy, and more emotional problems [10]. Poor sleep can cause severe fatigue among cancer patients [11], and it affects the course of the disease and survival [12]. It is, however, frequently unrecognized or poorly managed in clinical practice, and it receives very little attention [8].

Sleep disturbance in the general population is treated with medication [1]; however, in cancer patients, side-effects can significantly worsen cancer-related fatigue [12]. Because sleep disturbance is chronic, long-term, and safe non-pharmacological treatments are warranted.

Aerobic exercise (AE) may abate the physiological and psychological effects of cancer and its treatment. Among cancer patients, exercise can improve physical, functional, and social well-being, reduce symptom distress, and increase quality of life [13, 14]. Several reviews show inconsistent effects of exercise on sleep: while some see benefits in exercise [15, 16], others do not [17, 18]. Traditional theories of sleep function propose that exercise can promote sleep effectively via thermoregulation, body restoration, and energy conservation hypotheses [19]. The regulation of proinflammatory cytokines [20] and plasma concentrations of the mediators of sleep [21] may also modulate improvements in sleep quality after exercise.

Mind-body exercises (MBE), which involve a sequence of movements and postures with musculoskeletal stretching and relaxation, breath control, and mental focus, have gradually gained global popularity. Some reviewers have investigated the effects of MBE, such as yoga, qigong, and tai chi, among cancer patients, and concluded that they could improve quality of life, mood, stress level, immune function, and social functioning [22, 23]. Specifically, several meta-analyses have found positive effects of mind-body interventions, including MBE [16, 24] for sleep disturbance in cancer. However, one meta-analysis indicated a small and nonsignificant effect of yoga on sleep disturbances [23]. Some suggest that through the mindful practice of low-to-moderate intensity exercises, MBE strengthen one's mental awareness and elicit relaxation for better sleep [25, 26].

While both AE and MBE involve low physical risks [27] and low implementation costs [28], and both may relieve sleep disturbance in cancer patients, their effects have not been examined in cancer patients with sleep disturbances. Existing meta-analyses evaluating exercise's effects on sleep disturbances may be limited by floor effect, i.e., not using poor sleep as the entry criterion [13-18, 22-24]. Additionally, some meta-analyses included studies that were not randomized controlled trials (RCTs) [15-18, 29, 30]. These limitations greatly reduce the generalizability of the findings in clinical practice. To the best of our knowledge, this is the first comprehensive review and meta-analysis of the effectiveness of AE and MBE on sleep quality, based on RCTs in cancer patients with poor sleep. This review may inform clinical practice guidelines on implementing exercise regimes among cancer patients.

Objective

This review should provide healthcare professionals with evidence-based guidance on exercise prescriptions for managing sleep disturbance in cancer patients. The objectives were (1) to appraise the evidence on the effects of AE and MBE on sleep in cancer patients with disturbed sleep systematically; and (2) to conduct a meta-analysis of RCTs to determine the effectiveness of AE and MBE interventions on sleep in cancer patients with disturbed sleep.

Methods

Search strategy

The systematic review followed the guidance in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [31]. A comprehensive search of the literature was conducted in Medline, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, CINAHL, SportDiscus, and Web of Science. The databases were searched from the earliest date available through January 2018, using the search terms *cancer*, *exercise*, *mind-body*, and *randomized controlled trial*. For an example search strategy for Medline, see Table S1. We also hand-searched the reference lists of relevant studies to identify potential articles. The PRISMA flow chart is in Figure S1.

Eligibility criteria

To be eligible, the studies had to be RCTs, published as full papers in English. The inclusion criteria were studies involving adult patients (18 years and above), with any type of cancer diagnosis, and at any stage of the cancer care trajectory (before, during, or after treatment). Numerous forms of exercise interventions were eligible, and they were categorized as AE or MBE. AE studies targeted improvement in cardiovascular fitness, such as walking and treadmill, while MBE studies focused on the incorporation of mind and body, such as yoga, tai chi, and qigong. There were no restrictions on the frequency, intensity, or duration of the intervention, the setting, the presence or absence of supervision, and the follow-up time. Control groups could either be active (i.e., receiving another treatment related to health education or light exercise) or inactive (i.e., waitlist, no treatment, usual care). The studies needed to present at least one sleep measure, yet studies that used only some items from a questionnaire were excluded as nonstandard. Finally, only studies with a sample mean of sleep disturbance meeting meaningful cut-offs were included.

Meaningful cut-off scores for sleep disturbance

There are several measurement tools for sleep disturbance, both subjective and objective. The included studies used the Pittsburgh Sleep Quality Index (PSQI) and the General Sleep Disturbance Scale (GSDS) for subjective measures. PSQI is a 24-item scale that measures sleep disturbances during the past month along seven dimensions: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Adding the scores on these seven dimensions yields a global score. To be a poor sleeper, an individual's mean score must exceed the cut-off score of five [32]. GSDS is a 21-item scale that rates the frequency of sleep problems over the previous week [33]. Scores higher than the total cut-off score of 43 or a mean score of 3 distinguish poor sleepers [34, 35].

Objective measurements, like actigraphy, were commonly used for measuring sleep quality, by estimating sleep latency, wake after sleep onset, sleep efficiency, and total sleep time. Actigraphy monitoring period should be at least 3 days. Sleep disturbance was defined as one or more sleep-onset latency of more than 30 minutes, more than two waking episodes per night, a total sleep time of 6.5 hours or less, or sleep efficiency of 85% or less [36].

Only studies whose mean scores at baseline met these cut-offs in any one of the sleep parameters were included.

Study selection

The titles and abstracts of all articles were screened and counter-checked independently, by six reviewers in pairs of two (N.T., D.S.T.C., W.D., K.Y.H., J.L., and R.S.). A list of potentially relevant articles was generated, and the full-text articles were examined for eligibility against the selection criteria by four reviewers independently, in pairs of two (N.T., D.S.T.C, W.D., and K.Y.H.). The pairs discussed all inconsistencies and disagreements along the screening process.

Data extraction and quality assessment

Data extraction for all relevant studies was performed independently by three reviewers (N.T., D.S.T.C., and W.D.). All information regarding study characteristics (author, year, study design, year of publication), participant characteristics, intervention details (type, intensity, frequency, and intervention and control size), sleep quality measure used, and baseline and follow-up data, were recorded using a predesigned data-extraction form. When insufficient data or unclear presentations were found in the articles, the corresponding authors were contacted for clarification and data requests. Risks of bias were assessed using Cochrane's collaboration's risk of bias tool [37], using the domains of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. All data were verified and checked, discrepancies were discussed, and agreements on values were reached.

Data synthesis and statistical analyses

Our primary measure of the effect of interventions was the standardized mean difference (SMD) in change from baseline with 95% confidence intervals (CI) between intervention and control groups to assess differences in sleep quality. In studies with multiple measurements of sleep quality, we prioritized subjective measures of sleep quality; in studies that did not use subjective measures, we used sleep efficiency measured by actigraphy to measure sleep quality, since sleep efficiency is the most commonly used actigraphic parameter as the primary outcome measure in sleep disturbance research [38]. SMD and 95% CI were calculated for each study using the mean change difference from baseline to the last reported follow-up. For studies that did not report mean change and standard deviation (SD) of change, SMD was calculated from baseline and follow-up values of mean and SD, whereas the SD of difference was imputed based on a correlation coefficient (r) calculated from the studies, which presented means and SDs for change, baseline, and follow-up measurements (e.g., r=0.58 from Mustian et al., 2013 [39] for MB studies and r=0.52 from Rogers et al., 2017 [40] for AE studies). These methods of calculation were in line with the Cochrane handbook for imputing data for SMD in systematic reviews (Chapters 7.7.3.3 and 16.1.3.2) [37]. For PSQI, a positive difference indicated more inferior sleep quality. Therefore, the SMD for PSQI was inverted so that all effect sizes showed positive differences in intervention against control, indicating better sleep quality.

Four random-effects meta-analyses were used to compare the pooled effectiveness of (1) AE interventions against controls and (2) MBE interventions against controls at two timepoints: post-intervention and 3-6 months follow-up. For interventions that had more than one data collection point at 3-6 months follow-up, data at the earliest time point was included in the analysis because the latter follow-up point(s) had more drop-outs. Heterogeneity was investigated in each analysis using I^2 values. Pooled effect sizes are reported by SMD and 95% CI. Meta-regressions were performed for sensitivity analysis to evaluate heterogeneity further in terms of the study characteristics. We performed individual regression models for total intervention time, the number of follow-up weeks, study sample size (n<20 in all arms vs. larger sample sizes), risk of selection bias (low risk vs. high or unclear risk), and adherence (high vs. low, as indicated in the next section). We performed sensitivity analysis using a leave-one-out analysis to test whether individual studies influenced the results disproportionately. We used a trim-and-fill approach and funnel plots to investigate possible publication bias. We reported estimated pooled SMD from the trim-and-fill analysis. The trim-and-fill analysis adjusted the estimated pooled SMD based on the funnel plot as a measurable impact on possible publication bias (asymmetry of the funnel plot). All analyses of pooled effectiveness were conducted in STATA version 14.1.

Feasibility and safety assessment

Feasibility was determined by adherence, dropout rates, and occurrence of adverse events in participants. The adherence rate was generated by dividing the number of intervention sessions attended by the total number of sessions (including supervised and home-based, if applicable). Adherence reporting varied across studies. In this paper, high adherence was an average of 75% sessions attended, or >75% attended at least 80% of the classes or >60% attended all classes. The dropout rate was the number of dropped out patients at the last follow-up time point divided by the total number of patients in that arm.

Results

Study selection

The search generated 54,218 citations, of which 11,947 were potentially relevant. Of these, 11,904 were excluded, leaving 43 eligible RCTs for full-text review. Thirty-two were included in the qualitative analysis, whereas 27 were included in the meta-analysis, with reasons stated in Figure S1.

Characteristics of the studies

Table S2 summarizes the characteristics of the 32 RCTs. The sample sizes ranged from 16 to 410, and the analysis included data on 3,232 participants, of whom 1,714 randomly received AE or MBE. Participants in the intervention groups received either AE or MBE, while those in the control groups were either active (e.g., sham qigong, light exercise group, health education) or inactive (i.e., waitlist, or usual care). In total, there were 18 (56%) AE studies [40, 42-58] and 14 (44%) MBE studies [39, 41, 59-70]. Four (13%) trials [44, 60, 62, 64] used three-arm RCTs that included two groups receiving different interventions alongside a control group, or they involved two control groups (active and inactive). Eight trials (25%) had sleep as the primary outcome of the study. Twenty-two trials (69%) used only subjective sleep measures, three (9%) used an objective sleep measure, and seven (22%) used a combination. PSQI was the most common subjective sleep measure (n=27; 93%), whereas two studies used GSDS. Actigraphy was the only objective sleep measure. Regarding follow-up time, fifteen out of the 27 studies included in the meta-analysis did not have a 3-6 month post-intervention time frame (11 AE interventions, 4 MB interventions). The remaining twelve studies had follow-up at 3-6 months post-intervention in addition to the post-intervention time point (4 AE interventions, 8 MB interventions).

Participant characteristics

Table S2 also provides information about the participants. The mean ages of the participants ranged from 45-68, with an average SD ranging from 1.32 to 14.6. Nineteen (59%) trials involved solely female cancer patients, and one involved only male cancer patients. Nineteen (59%) studies involved breast cancer patients. Early-stage cancer patients (0-III) were most commonly included in the studies, although not every study reported the cancer stage. Twelve (38%) involved cancer patients who had completed treatment and 10 recruited patients scheduled for treatment.

At baseline, all participants had sleep disturbance mean scores greater than the cut-off (Table S3). In PSQI studies, the baseline scores ranged from 6.2-13.42, and 5.22-13.17 in the intervention and control groups, respectively. For the GSDS studies, one yielded a total score of 70.5 [41] and the other a mean score of 3.45 [42]. For studies using actigraphy only, the range of sleep efficiency was 79.7-84.4% and 80.4-85.2% in intervention and control groups, respectively [44, 55].

Aerobic exercise interventions

Table S4 summarizes the AE interventions (n=18). There were variations in the types and duration of AE interventions. Half the studies only used AE; the other half combined AE with resistance exercise, behavioral support sessions, or individualized diet advice. Walking was the most typical form of AE (n=15; 83%), while other studies used a cycle ergometer or a treadmill (n=3). The duration of the interventions varied from 4-24 weeks, but most prescribed 12 weeks; the frequency ranged from one to five times per week. Ghavami et al. [46] encouraged patients to attend five 50-minute supervised exercise sessions each week for 24 weeks, plus weekly individualized diet counseling that aimed at steady weight loss. Nine trials (28%) involved home-based exercise, while five (16%) were supervised, followed by home-based. All supervised sessions used a group format. In the five home-based exercise trials [42, 45, 53, 54, 57], researchers conducted weekly phone calls to monitor adherence and to discuss exercise prescription.

Exercise intensity varied from low to high. Most studies (n=17; 53%) adopted moderate intensity exercise. Seven trials used percentage of heart rate reserve or target heart rate ranging from 40%-85% depending on the level of intensity [36, 43, 45, 46, 54, 55, 58]. Three trials employed Borg's rating of perceived exertion [42, 51, 52], while another used metabolic equivalent of task (h/week) [47].

Mind-body exercise interventions

Table S4 summarizes the MBE interventions (n=14). Among the 14 trials, nine (64%) used yoga, one (7%) used yoga breathing practice only, three (21%) used qigong and tai chi, and one used dance movement therapy.

McQuade et al. [60] employed the classical eight-form Yang-style tai chi; Larkey et al. [59] employed tai chi easy, together with qigong exercises; and Chen et al. [65] used a modified version of medical qigong developed by Guo Lin (Gou Lin New Qigong). Ho et al. [68] used dance movement therapy, which was a movement-based psychosocial intervention incorporating therapeutic components of dance and group psychotherapy. The duration of the MBE varied from 3-12 weeks, and the time per week ranged from 75-200 minutes (with one trial not reporting the length of the class). Class frequency varied from once a month to five times a week. Chaoul et al. [64] had patients participating in four sessions of yoga during their 12-week chemotherapy, followed by three booster sessions over the subsequent six months, while Larkey et al. [59] arranged classes twice a week for the first two weeks, followed by once a week for the remaining ten weeks. All remaining studies had regular classes throughout the intervention.

Only one study reported a low-intensity exercise [67]. However, none measured exercise intensity. Most trials (n=9; 64%) had group classes, three had either one-to-one or group classes, and the rest had one-to-one classes. Nine trials (64%) encouraged self-practice at home in addition to supervised classes.

Feasibility and safety assessment

All but ten trials reported adherence information, with 16 (50%) reporting high adherence rates, including trials with long interventions. The dropout rates ranged from 0-61.5%, and the trial with the highest dropout rate had the longest follow-up period after the intervention. The dropout rates in the control groups ranged from 0% (attention control) to 50.9% (health education control). Common reasons for dropout were deterioration in physical condition and reduced or no interest in the assigned groups. Fourteen studies did not report the presence or absence of any adverse events during the intervention period. Ten studies reported no adverse events or adverse events unrelated to exercise, while one yoga study [67] reported minor adverse events in seven participants, six of whom recovered without treatment, and one recovered with the use of analgesic drugs.

Description of the study results

Summary of outcomes

Aerobic exercise intervention

The PSQI and GSDS scores in the intervention groups improved in all studies except Wenzel et al. [57] and Rogers 2009 et al. [50]. Sleep efficiency improved in Roveda et al. [44], but it decreased in Coleman et al. 2012 [55], which only used an objective measure. In studies with multiple measures, Rogers et al. 2015 [58] and Rogers et al. 2017 [40] found both subjective and objective improvements in the intervention groups. Nevertheless, Chen et al. [45] and Rogers et al. 2013 [56] found improvements in PSQI, but no improvements or poorer results in sleep efficiency.

Mind-body exercise intervention

PSQI scores improved in the intervention groups in all studies. Studies with multiple sleep measures had consistent results. In Mustian et al. [39] and Chaoul et al. [64], both PSQI scores and sleep efficiency, as measured by actigraphy, improved.

Meta-analysis of RCTs

Risk of bias

A summary of risk of bias is in Table S5. Most studies had a low risk for the domains of random sequence generation, selective outcome reporting, and incomplete outcome data.

Almost half of the studies did not have sufficient information to determine the risk of bias for allocation concealment. Participants were only blinded in one study, which used sham qigong in the control condition [59]. Six trials had the outcome assessor and the statistician blinded.

Effects on sleep

Aerobic exercise interventions

Fifteen studies were included for comparison of AE interventions and controls (intervention participants, n=774; control participants, n=669). A total of 16 comparisons were made at the post-intervention timepoint, because one study had two exercise intervention arms (high intensity and low-to-moderate intensity) against control [43]. AE interventions at post-intervention yielded an overall significant result in improving sleep (SMD=0.33, 95% CI: 0.11, 0.54), but heterogeneity was large (I^2=70.0%, p<0.01) (Figure 1). The meta-regression displayed no effects of heterogeneity in total intervention time, follow-up weeks, publication year, baseline sleep quality, sample size, intervention adherence, or high risk of selection bias. At 3-6 months follow-up, AE interventions showed a significant benefit for sleep quality compared to control (SMD=0.37, 95% CI: 0.18, 0.55) among four studies, heterogeneity between studies was not present at six months follow-up (I^2=0%, p=0.636) (Figure 2).

Ghavami et al. [46] had a disproportionate impact on the results at 3-6 months follow-up in the leave-one-out sensitivity analysis for the AE studies. Thus, it was excluded from the pooled analysis in the 6-month analysis.

Mind-body exercise interventions

Twelve studies were included in the analysis (intervention participants, n=768; control participants, n=681). Overall, the pooled effect of MBE post-intervention favored intervention (SMD=0.18; 95% CI: 0.06, 0.30), with very low heterogeneity between studies

(I^2=0.0%, p=0.953) (Figure 3). At 3-6 months follow-up, analysis of eight studies showed that there was no difference between MBE interventions and controls (SMD=0.02, 95% CI: -0.14, 0.18), and again no heterogeneity was observed (I^2=0%, p=0.522) (Figure 4). The leave-one-out sensitivity analysis did not identify any MBE studies with a disproportionate impact on the results.

In the sensitivity analyses for publication bias for studies on AE and MBE interventions, the funnel plots had slight asymmetry, suggesting some publication bias (Figure S2 and S3). The trim-and-fill approach did not trim or fill any studies for both AE and MBE interventions; thus, the results of the trim-and-fill approach meta-analysis remained unchanged.

Discussion

Summary of evidence

We have summarized the available empirical evidence on the effects of AE and MBE on sleep outcomes in patients with cancer of any type, of any stage, who were at any point in the treatment trajectory, and who experienced sleep disturbance. Our meta-analysis included 27 studies with a total of 2,892 participants, of which 15 and 12 trials used AE and MBE, respectively. The pooled effect sizes suggested that both AE and MBE interventions significantly improved sleep in cancer patients with sleep disturbance. The significant effect remained after 3-6 months for AE, while MBE did not show a significant effect after 3-6 months. To our knowledge, this is the first meta-analysis to analyze the effect of exercise on sleep among cancer patients by adopting stringent inclusion criteria and only including studies with participants falling below meaningful cut-offs for various sleep parameters.

We found that AE interventions improved sleep among cancer patients experiencing sleep disturbance. The benefits were still evident at 3-6 months post-intervention. Nevertheless, heterogeneity was high in the analysis for the post-intervention time point, and meta-regression failed to identify factors leading to the high heterogeneity. Of note, half the reviewed AE interventions were combined with other components, such as resistance exercise, behavioral support sessions, or individualized diet advice; and they are delivered in mixed modes, such as supervised solely, home-based solely, or supervised followed by home-based. It is not possible to provide any definitive recommendation about the optimal exercise prescription from this review. Future studies are warranted to identify the optimal aerobic exercise modalities on improving sleep outcomes.

MBE interventions had significant effects on sleep outcomes post-intervention; however, the effects diminished 3-6 months after the intervention. Among the five studies with no positive findings at 3-6 months post-intervention, four demonstrated significant intervention benefits post-treatment [60, 62-64]. These four studies included patients undergoing or scheduled for cancer treatment (i.e., radiotherapy or chemotherapy), with treatment-related high levels of fatigue, more physical symptoms, and poor activity tolerance [71]. After the study, patients may not maintain self-practice due to the treatment burden, leading to the disappearance of intervention effects at follow-up. Thus, a conventional supervised approach is preferred for future studies targeting patients receiving cancer treatment to deliver MBE interventions. Meanwhile, future research should adopt rigorous designs to identify the essential components of MBE to make the intervention effect sustainable.

Finally, most studies adopted only self-reported, subjective measures for assessing sleep disturbance, while a few complemented their findings using actigraphy as an objective measure. Although sleep disturbance is a subjective phenomenon [72], increasing attention has gone to objective measures of sleep and circadian rhythms. Further interventional research, including both subjective and objective outcome measures, is warranted. In addition, immune markers should be included in future research to examine the possible underlying mechanisms of exercise interventions on sleep.

Clinical Implications

There were no evident detrimental effects on sleep or serious adverse events due to intervention for either AE or MBE. Both AE and MBE improved sleep post-intervention among cancer patients with poor sleep. The effects of MBE interventions targeting patients receiving cancer treatment were not sustained after the study. Thus, a conventional supervised approach is recommended for delivering MBE interventions among cancer patients undergoing treatment. Due to the high heterogeneity in the reviewed AE studies, knowledge of which exercise prescription has optimal effects would improve clinical decision-making and enhance the practical applicability of the findings.

Strengths and limitations

This study is the first to review the literature on exercise interventions to improve sleep in cancer patients by focusing on poor sleepers systematically. Since a substantial proportion of RCTs did not exclusively screen for patients with sleep problems by screening methods, we used an open approach to include all relevant studies during the initial search. Then we selected studies with participants falling below clinically meaningful cut-offs of sleep parameters. This comprehensive approach allowed us to identify studies with an important proportion of poor sleepers at baseline. However, caution is necessary in that some participants in the included studies may not have shown sleep problems, even though the sample mean baseline sleep scores met the cut-offs. In addition, despite the strenuous effort to perform a comprehensive literature search, it is possible that relevant studies were missed. Another limitation is the high heterogeneity in the AE interventions, which could not be explained by the meta-regressions. Besides, the measurement time frame of actigraphy is inconsistent, ranging from 3 days to 7 days. Finally, over half of the studies included only breast cancer patients, and only full studies published in English were included, which limit the generalizability of the findings.

Conclusions

Both AE and MBE are beneficial and safe to improve sleep among cancer patients with sleep disturbances. The significant effect remained at 3-6 months post-intervention for AE, but not for MBE. Future studies could explore the optimal AE approach for improving sleep outcomes. For MBE, future research should identify essential components to make the intervention effect sustainable.

Practice Points

1. Both aerobic and mind-body exercises had a positive impact on improving sleep outcomes in cancer patients with poor sleep.
2. The benefits of aerobic exercises for sleep outcomes are sustained 3-6 months after the intervention.
3. As aerobic and mind-body exercises appear to cause no detrimental effects, both appear safe for cancer patients at any stage and treatment phase.
4. A regular supervised approach is recommended for delivering mind-body exercises interventions among patients undergoing treatment.

Research Agenda

1. Both subjective and objective outcome measures should be employed to measure sleep.
2. Future studies should explore and standardize the optimal aerobic exercises prescription.
3. Rigorous RCTs should be adopted to identify the essential components of mind-body exercises to sustain the improvement in sleep outcomes after completion of the study.

References

*1. Berger AM, Parker KP, Young-McCaughan S, Mallory GA, Barsevick AM, Beck SL, et al. Sleep/wake disturbances in people with cancer and their caregivers: state of the science. *Oncol Nurs Forum* 2005; **32**(6):E98-126.
2. Fiorentino L, Ancoli-Israel S. Insomnia and its treatment in women with breast cancer. *Sleep Medicine Reviews* 2006; **10**(6): 419-29.
3. Palesh O, Peppone L, Innominato PF, Janelsins M, Jeong M, Sprod L, et al. Prevalence, putative mechanisms, and current management of sleep problems during chemotherapy for cancer. *Nature and Science of Sleep* 2012; **4**: 151.
4. Chen M-L, Yu C-T, Yang C-H. Sleep disturbances and quality of life in lung cancer patients undergoing chemotherapy. *Lung Cancer* 2008; **62**(3): 391-400.
5. Ginsburg ML, Quirt C, Ginsburg AD, MacKillop WJ. Psychiatric illness and psychosocial concerns of patients with newly diagnosed lung cancer. *CMAJ: Canadian Medical Association Journal* 1995; **152**(5): 701.
6. Kvale EA, Shuster JL. Sleep disturbance in supportive care of cancer: a review. *Journal of Palliative Medicine* 2006; **9**(2): 437-50.
7. Palesh OG, Roscoe JA, Mustian KM, Roth T, Savard J, Ancoli-Israel S, et al. Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center–Community Clinical Oncology Program. *Journal of Clinical Oncology* 2010; **28**(2): 292.
8. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. Journal of clinical oncology. 2001; **19**(3): 895-908.
9. Deimling GT, Bowman KF, Sterns S, Wagner LJ, Kahana B. Cancer-related health worries and psychological distress among older adult, long-term cancer survivors. *Psycho-Oncology* 2006; **15**(4): 306-20.
10. Fortner BV, Stepanski EJ, Wang SC, Kasprowicz S, Durrence HH. Sleep and quality of life in breast cancer patients. *Journal of Pain and Symptom Management* 2002; **24**(5): 471-80.
11. Anderson KO, Getto CJ, Mendoza TR, Palmer SN, Wang XS, Reyes-Gibby CC, et al. Fatigue and sleep disturbance in patients with cancer, patients with clinical depression, and community-dwelling adults. *Journal of Pain and Symptom Management* 2003; **25**(4): 307-18.
12. Dahiya S, Ahluwalia MS, Walia HK. Sleep disturbances in cancer patients: underrecognized and undertreated. *Cleve Clin J Med* 2013; **80**(11): 722-32.
13. Ni H-J, Pudasaini B, Yuan X-T, Li H-F, Shi L, Yuan P. Exercise training for patients pre-and postsurgically treated for non-small cell lung cancer: a systematic review and meta-analysis. *Integrative Cancer Therapies* 2017; **16**(1): 63-73.
14. Knols R, Aaronson NK, Uebelhart D, Fransen J, Aufdemkampe G. Physical exercise in cancer patients during and after medical treatment: a systematic review of randomized and controlled clinical trials. *Journal of Clinical Oncology* 2005; **23**(16): 3830-42.
15. Chiu H-Y, Huang H-C, Chen P-Y, Hou W-H, Tsai P-S, editors. Walking improves sleep in individuals with cancer: a meta-analysis of randomized, controlled trials. *Oncol Nurs Forum* 2015;**42**(2):E54-62.
*16. Papadopoulos D, Papadoudis A, Kiagia M, Syrigos K. Nonpharmacologic interventions for improving sleep disturbances in patients with lung cancer: a systematic review and meta-analysis. *J Pain Symptom Manage* 2018; **55**(5): 1364-81.e5.
17. Langford DJ, Lee K, Miaskowski C. Sleep disturbance interventions in oncology patients and family caregivers: a comprehensive review and meta-analysis. *Sleep Medicine Reviews* 2012; **16**(5): 397-414.

*18. Mercier J, Savard J, Bernard P. Exercise interventions to improve sleep in cancer patients: a systematic review and meta-analysis. *Sleep Medicine Reviews* 2017; **36**: 43-56.
19. Berger R, Phillips N. Comparative aspects of energy metabolism, body temperature and sleep. *Acta Physiologica Scandinavica Supplementum* 1988; **574**: 21-7.
20. Driver HS, Taylor SR. Exercise and sleep. *Sleep Medicine Reviews* 2000; **4**(4): 387-402.
21. Santos RVT, Tufik S, de Mello MT. Exercise, sleep and cytokines: is there a relation? *Sleep Medicine Reviews* 2007; **11**(3): 231-9.
22. Zeng Y, Luo T, Xie H, Huang M, Cheng ASK. Health benefits of qigong or tai chi for cancer patients: a systematic review and meta-analyses. *Complementary Therapies in Medicine* 2014; **22**(1): 173-86.
23. Buffart LM, van Uffelen JG, Riphagen II, Brug J, van Mechelen W, Brown WJ, et al. Physical and psychosocial benefits of yoga in cancer patients and survivors: a systematic review and meta-analysis of randomized controlled trials. *BMC Cancer* 2012; **12**(1): 559.
*24. Chiu H-Y, Chiang P-C, Miao N-F, Lin E-Y, Tsai P-S. The effects of mind-body interventions on sleep in cancer patients: a meta-analysis of randomized controlled trials. *Journal of Clinical Psychiatry* 2014; **75**(11):1215-23.
25. Lou L, Zou L, Fang Q, Wang H, Liu Y, Tian Z, et al. Effect of taichi softball on function-related outcomes in older adults: a randomized control trial. *Evidence-Based Complementary and Alternative Medicine* 2017;**2017**:1-9.
26. Zou L-Y, Wang C-Y, Wang H-R. Effect of a long-term modified tai chi-based intervention in attenuating bone mineral density in postmenopausal women in southeast China: Study protocol for a randomized controlled trial. C*linical Trials in Degenerative Diseases* 2017; **2**(3): 46.
27. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvão DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Medicine & Science in Sports & Exercise* 2010; **42**(7): 1409-26.
28. Caudill M, Schnable R, Zuttermeister P, Benson H, Friedman R. Decreased clinic use by chronic pain patients: response to behavioral medicine intervention. *Clinical Journal of Pain* 1991; **7**(4): 305-10.
*29. Mishra SI, Scherer RW, Geigle PM, Berlanstein DR, Topaloglu O, Gotay CC, et al. Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database of Systematic Reviews* 2012; **2012**(8): CD007566.
30. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database of Systematic Reviews* 2012; **2012**(8): CD008465.
31. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009; **6**(7): e1000097.
32. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research* 1989; **28**(2): 193-213.
33. Lee K, Cho M, Miaskowski C, Dodd M. Impaired sleep and rhythms in persons with cancer. *Sleep Medicine Reviews* 2004; **8**(3): 199-212.
34. Lee KA. Self-reported sleep disturbances in employed women. *Sleep* 1992; **15**(6): 493-8.
35. Lee S-Y. Validating the general sleep disturbance scale among Chinese American parents with hospitalized infants. *Journal of Transcultural Nursing* 2007; **18**(2): 111-7.

36. Wang S-Y, Chang H-J, Lin C-C. Sleep disturbances among patients with non-small cell lung cancer in Taiwan: congruence between sleep log and actigraphy. *Cancer Nursing* 2010; **33**(1): E11-E17.
37. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Hoboken, NJ: Wiley 2008.
38. Reed DL, Sacco WP. Measuring sleep efficiency: what should the denominator be? *Journal of Clinical Sleep Medicine* 2016; **12**(2): 263-6.
39. Mustian KM, Sprod LK, Janelsins M, Peppone LJ, Palesh OG, Chandwani K, et al. Multicenter, randomized controlled trial of yoga for sleep quality among cancer survivors. *Journal of Clinical Oncology* 2013; **31**(26): 3233.
40. Rogers LQ, Courneya KS, Oster RA, Anton PM, Robbs RS, Forero A, et al. Physical activity and sleep quality in breast cancer survivors: a randomized trial. *Medicine and Science in Sports and Exercise* 2017; **49**(10): 2009.
41. Dhruva A, Miaskowski C, Abrams D, Acree M, Cooper B, Goodman S, et al. Yoga breathing for cancer chemotherapy-associated symptoms and quality of life: results of a pilot randomized controlled trial. *Journal of Alternative and Complementary Medicine* 2012; **18**(5): 473-9.
42. Naraphong W, Lane A, Schafer J, Whitmer K, Wilson BR. Exercise intervention for fatigue-related symptoms in Thai women with breast cancer: a pilot study. *Nursing & Health Sciences* 2015; **17**(1): 33-41.
43. Kampshoff CS, Chinapaw MJ, Brug J, Twisk JW, Schep G, Nijziel MR, et al. Randomized controlled trial of the effects of high intensity and low-to-moderate intensity exercise on physical fitness and fatigue in cancer survivors: results of the Resistance and Endurance exercise After ChemoTherapy (REACT) study. *BMC Medicine* 2015; **13**(1): 275.
44. Roveda E, Vitale JA, Bruno E, Montaruli A, Pasanisi P, Villarini A, et al. Protective effect of aerobic physical activity on sleep behavior in breast cancer survivors. *Integrative Cancer Therapies* 2017; **16**(1): 21-31.
45. Chen H-M, Tsai C-M, Wu Y-C, Lin K-C, Lin C-C. Effect of walking on circadian rhythms and sleep quality of patients with lung cancer: a randomised controlled trial. *British Journal of Cancer* 2016; **115**(11): 1304.
46. Ghavami H, Akyolcu N. The impact of lifestyle interventions in breast cancer women after completion of primary therapy: a randomized study. *European Journal of Breast Health* 2017; **13**(2): 94-100.
47. Dhillon H, Bell ML, van der Ploeg H, Turner J, Kabourakis M, Spencer L, et al. Impact of physical activity on fatigue and quality of life in people with advanced lung cancer: a randomized controlled trial. *Annals of Oncology* 2017; **28**(8): 1889-97.
48. Coleman EA, Coon S, Hall-Barrow J, Richards K, Gaylor D, Stewart B. Feasibility of exercise during treatment for multiple myeloma. *Cancer Nursing* 2003; **26**(5): 410-9.
49. Payne JK, Thorpe J, Held J, Shaw H, eds. Impact of exercise on biomarkers, fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer. *Oncology Nursing Forum* 2007; **35**(4): 635-42.
50. Rogers LQ, Hopkins-Price P, Vicari S, Pamenter R, Courneya KS, Markwell S, et al. A randomized trial to increase physical activity in breast cancer survivors. *Medicine & Science in Sports & Exercise* 2009; **41**(4): 935-46.
51. Sprod LK, Palesh OG, Janelsins MC, Peppone LJ, Heckler CE, Adams MJ, et al. Exercise, sleep quality, and mediators of sleep in breast and prostate cancer patients receiving radiation therapy. *Community Oncology* 2010; **7**(10): 463.
52. Tang M-F, Liou T-H, Lin C-C. Improving sleep quality for cancer patients: benefits of a home-based exercise intervention. *Supportive Care in Cancer* 2010; **18**(10): 1329-39.

53. Donnelly C, Blaney J, Lowe-Strong A, Rankin J, Campbell A, McCrum-Gardner E, et al. A randomised controlled trial testing the feasibility and efficacy of a physical activity behavioural change intervention in managing fatigue with gynaecological cancer survivors. *Gynecologic Oncology* 2011; **122**(3): 618-24.
54. Wang Y-J, Boehmke M, Wu Y-WB, Dickerson SS, Fisher N. Effects of a 6-week walking program on Taiwanese women newly diagnosed with early-stage breast cancer. *Cancer Nursing* 2011; **34**(2): E1-E13.
55. Coleman EA, Goodwin JA, Kennedy R, Coon SK, Richards K, Enderlin C, et al., eds. Effects of exercise on fatigue, sleep, and performance: a randomized trial. *Oncology Nursing Forum* 2012; **39**(5): 468-77. NIH Public Access.
56. Rogers LQ, Fogleman A, Trammell R, Hopkins-Price P, Vicari S, Rao K, et al. Effects of a physical activity behavior change intervention on inflammation and related health outcomes in breast cancer survivors: pilot randomized trial. *Integrative Cancer Therapies* 2013; **12**(4): 323-35.
57. Wenzel JA, Griffith KA, Shang J, Thompson CB, Hedlin H, Stewart KJ, et al. Impact of a home-based walking intervention on outcomes of sleep quality, emotional distress, and fatigue in patients undergoing treatment for solid tumors. *Oncologist* 2013; **18**(4): 476.
58. Rogers LQ, Fogleman A, Trammell R, Hopkins-Price P, Spenner A, Vicari S, et al. Inflammation and psychosocial factors mediate exercise effects on sleep quality in breast cancer survivors: pilot randomized controlled trial. *Psycho-Oncology* 2015; **24**(3): 302-10.
59. Larkey LK, Roe DJ, Weihs KL, Jahnke R, Lopez AM, Rogers CE, et al. Randomized controlled trial of qigong/tai chi easy on cancer-related fatigue in breast cancer survivors. *Annals of Behavioral Medicine* 2014; **49**(2): 165-76.
60. McQuade JL, Prinsloo S, Chang DZ, Spelman A, Wei Q, Basen-Engquist K, et al. Qigong/tai chi for sleep and fatigue in prostate cancer patients undergoing radiotherapy: a randomized controlled trial. *Psycho-Oncology* 2017; **26**(11): 1936-43.
61. Bower JE, Garet D, Sternlieb B, Ganz PA, Irwin MR, Olmstead R, et al. Yoga for persistent fatigue in breast cancer survivors: a randomized controlled trial. *Cancer* 2012; **118**(15): 3766-75.
62. Chandwani KD, Perkins G, Nagendra HR, Raghuram NV, Spelman A, Nagarathna R, et al. Randomized, controlled trial of yoga in women with breast cancer undergoing radiotherapy. *Journal of Clinical Oncology* 2014; **32**(10): 1058.
63. Chandwani KD, Thornton B, Perkins GH, Arun B, Raghuram N, Nagendra H, et al. Yoga improves quality of life and benefit finding in women undergoing radiotherapy for breast cancer. *Journal of the Society for Integrative Oncology* 2010; **8**(2): PAGE-PAGE.
64. Chaoul A, Milbury K, Spelman A, Basen-Engquist K, Hall MH, Wei Q, et al. Randomized trial of Tibetan yoga in patients with breast cancer undergoing chemotherapy. *Cancer* 2018; **124**(1): 36-45.
65. Chen Z, Meng Z, Milbury K, Bei W, Zhang Y, Thornton B, et al. Qigong improves quality of life in women undergoing radiotherapy for breast cancer: results of a randomized controlled trial. *Cancer* 2013; **119**(9): 1690-8.
66. Cohen L, Warneke C, Fouladi RT, Rodriguez MA, Chaoul-Reich A. Psychological adjustment and sleep quality in a randomized trial of the effects of a Tibetan yoga intervention in patients with lymphoma. *Cancer* 2004; **100**(10): 2253-60.
67. Cramer H, Pokhrel B, Fester C, Meier B, Gass F, Lauche R, et al. A randomized controlled bicenter trial of yoga for patients with colorectal cancer. *Psycho-Oncology* 2016; **25**(4): 412-20.
68. Ho RT, Fong TC, Cheung IK, Yip PS, Luk M-Y. Effects of a short-term dance movement therapy program on symptoms and stress in patients with breast cancer undergoing

radiotherapy: a randomized, controlled, single-blind trial. *Journal of Pain and Symptom Management* 2016; **51**(5): 824-31.
69. Danhauer SC, Mihalko SL, Russell GB, Campbell CR, Felder L, Daley K, et al. Restorative yoga for women with breast cancer: findings from a randomized pilot study. *Psycho-Oncology*. 2009; **18**(4): 360-8.
70. Kiecolt-Glaser JK, Bennett JM, Andridge R, Peng J, Shapiro CL, Malarkey WB, et al. Yoga's impact on inflammation, mood, and fatigue in breast cancer survivors: a randomized controlled trial. *Journal of Clinical Oncology* 2014; **32**(10): 1040.
71. Yang YH. [Trajectory of fatigue, quality of life and physical symptoms in cancer patients receiving radiotherapy]. *Taehan Kanho Hakhoe Chi* 2003; **33**(5): 562-9.
72. Morin CM. The nature of insomnia and the need to refine our diagnostic criteria. *Psychosomatic Medicine* 2000; **62**(4): 483-5.

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