TITLE: Mind and Body Practices for Fatigue Reduction in Patients with Cancer and Hematopoietic Stem Cell Transplant Recipients: A Systematic Review and Meta-Analysis

RUNNING HEAD: Mind and body practices for fatigue

AUTHORS: Nathan Duong ^a, Hailey Davis ^a, Paula D Robinson ^b, Sapna Oberoi ^b, Danielle Cataudella ^c, S Nicole Culos-Reed ^d, Faith Gibson ^e, Miriam Götte ^f, Pamela Hinds ^g, Sanne L Nijhof ^h, Deborah Tomlinson ^a, Patrick van der Torre ^h, Elena Ladas ⁱ, Sandra Cabral ^b, L Lee Dupuis ^{a,j}, and Lillian Sung ^{a,k,*}

AFFILIATIONS:

^a Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, ON

^b Pediatric Oncology Group of Ontario, Toronto, ON

^c Department of Pediatric Psychology, Children's Hospital, London Health Sciences Centre, London, ON

^d Faculty of Kinesiology, University of Calgary, Calgary, AB

^e Centre for Outcomes and Experiences Research in Children's Health, Illness, and Disability, Great Ormond Street Hospital for Children NHS Foundation Trust, London, and School of Health Sciences, University of Surrey, Guildford, UK

^f University Hospital Essen, Center for Child and Adolescent Medicine, Department of Pediatric Hematology/Oncology, Essen, Germany

^g Department of Nursing Science, Professional Practice, and Quality, Children's National Health System, Washington, District of Columbia, USA; Department of Pediatrics, George Washington University, Washington, District of Columbia, USA.

^h Division of Pediatrics, Wilhelmina Children's Hospital (part of UMC Utrecht), Utrecht, Netherlands

ⁱ Division of Pediatric Hematology/Oncology/Stem Cell Transplant, Institute of Human Nutrition, and Mailman School of Public Health, Department of Epidemiology, Columbia University Medical Center, New York, NY

^j Department of Pharmacy, The Hospital for Sick Children, and Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON

^k Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, ON

***Corresponding Author:**

Lillian Sung, MD, PhD, Division of Haematology/Oncology

The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G1X8

Telephone: 416-813-5287

Fax: 416-813-5979

Email: lillian.sung@sickkids.ca

Word Counts: Abstract 150; Text 2562; Table 4; Figures 2; Appendices 4

Key words: fatigue, hematopoietic stem cell transplant, randomized control trials, mindfulness, acupuncture therapy, acupressure, relaxation therapy, massage

Contributors:

Study concept: ND, HD, SO, PR, LS

Study design: ND, HD, SO, PR, LS

Data acquisition: ND, HD, SO, PR, LS

Quality control: ND, HD, PR, LS

Data analysis and interpretation: ND, HD, PR, LS

Statistical analysis: ND, HD, PR, LS

Manuscript preparation: ND, HD, PR, LS

Manuscript editing: All

Manuscript review and approval of the final version: All

TABLE OF CONTENTS

Section	Page
Abstract	2
Introduction	3
Methods and Materials	4
Results	8
Discussion	10
References	13
Tables	16
Figures	23

ABSTRACT

Purpose: To determine whether non-physical activity mind and body practices reduce the severity of fatigue in patients with cancer or hematopoietic stem cell transplant (HSCT) recipients compared to control interventions.

Methods: We included randomized trials which compared non-physical activity mind and body practices compared with control interventions for the management of fatigue in cancer and HSCT patients.

Results: Among 55 trials (4975 patients), interventions were acupuncture or acupressure (n=12), mindfulness (n=11), relaxation techniques (n=10), massage (n=6), energy therapy (n=5), energizing yogic breathing (n=3) and others (n=8). When combined, all interventions significantly reduced fatigue severity compared to all controls (standardized mean difference -0.51, 95% confidence interval -0.73 to -0.29). More specifically, mindfulness and relaxation significantly reduced fatigue severity.

Conclusions: Mindfulness and relaxation were effective at reducing fatigue severity in patients with cancer and HSCT recipients. Future studies should evaluate how to translate these findings into clinical practice across different patient groups.

INTRODUCTION

Cancer-related fatigue (CRF) is a distressing, persistent and subjective sense of tiredness related to cancer or cancer treatments that interferes with usual functioning.[1] CRF is highly prevalent and can occur throughout the treatment trajectory.[2-5] The cause of CRF is multifactorial and may be related to cancer itself, treatments and comorbidities.[1, 6] Hematopoietic stem cell transplantation (HSCT) recipients with and without cancer also experience severe fatigue.[7, 8] Fatigue is an important issue because it reduces quality of life and may lead to the decision to stop cancer treatments.[4, 5, 9]

Many approaches have been studied for the management of fatigue in cancer patients, including physical activity, psychological interventions and pharmacological approaches.[1, 10, 11] Another set of interventions include complementary health approaches.[12] The National Center for Complementary and Integrative Health categorizes complementary health approaches as: (1) natural products such as herbs, vitamins and minerals; (2) mind and body practices; and (3) other approaches including homeopathy and naturopathy. Studying complementary health approaches is important as patients and families are particularly interested in this therapeutic approach, particularly for symptom management.[13]

In the present analysis, we focused on evaluating non-physical activity mind and body practices for fatigue management. Among mind and body practices, yoga, tai chi, and qi gong can be classified as neuromotor physical activities[14] and were excluded from the present analysis. Consequently, our primary objective was to determine whether non-physical activity mind and body practices reduce the severity of fatigue among adults and children with cancer or HSCT recipients when compared to control interventions. Our secondary objective was to determine whether the effect of these

mind and body practices on fatigue varied by patient, intervention or methodological factors.

METHODS AND MATERIALS

For the conduct of this systematic review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[15] With the assistance of a library scientist, we searched for randomized trials indexed from 1980 to May 11, 2017 in the following electronic databases: MEDLINE, MEDLINE in-process, EMBASE, Cochrane Central Register of Controlled Trials, CINAHL, and PsychINFO. The search strategy included Medical Subject Heading terms and text words that identified patients with cancer or HSCT recipients who received an intervention to reduce fatigue. Appendix A shows the full search strategies.

Study Selection

Eligibility criteria were defined *a priori*. We included studies if participants of any age had cancer or were HSCT recipients, and if the study was a fully published primary randomized or quasi-randomized trial with a parallel group design. The study had to evaluate an intervention for the prevention or treatment of fatigue. We excluded studies if less than 75% of participants had cancer or were undergoing HSCT; if fatigue was either not an end-point or reported as an adverse effect; if the intervention was direct cancer treatment; and if less than five participants were randomized to any study arm. We did not restrict inclusion by language. For the purpose of this systematic review, we then limited studies to those in which non-physical activity mind and body practices were the intervention being evaluated.

Two reviewers (SO, PDR or LS) independently evaluated the titles and abstracts of studies identified by the search strategy. Any publication considered potentially

relevant by any reviewer was retrieved in full and assessed for eligibility by two reviewers (SO, PDR or LS). Inclusion of studies in this systematic review was determined by agreement of both reviewers. Discrepancies between the two reviewers were resolved by consensus and adjudication by a third reviewer if required (LLD or LS). Agreement in study inclusion between the two reviewers was described using the kappa statistic. Strength of agreement was defined as slight (0.00 to 0.20), fair (0.21 to 0.40), moderate (0.41 to 0.60), substantial (0.61 to 0.80), or almost perfect (0.81 to 1.00).[16]

Data Abstraction and Outcomes

Data were abstracted in duplicate by two reviewers (ND, HD or PDR) and any discrepancies were resolved by consensus. If discrepancies could not be resolved by consensus, a third reviewer (LS) adjudicated. We contacted authors in the event of missing primary outcome data.

The primary outcome was self-reported fatigue severity across the fatigue scales used in the primary studies. For studies that used more than one fatigue scale, we selected one scale to be used for analyses based upon an *a priori* developed rule. We selected the most prevalent fatigue scale used across studies (see Appendix B).

Categorization of Non-Physical Activity Mind and Body Practice Interventions and Control Groups

The interventions were non-physical activity mind and body practices. Practices were classified as: (1) acupuncture and acupressure; (2) mindfulness (practice of enhancing awareness of thoughts, emotions, and experiences);[17] (3) relaxation techniques (such as progressive muscle relaxation and guided imagery); (4) massage therapies; (5) energy therapies (including Reiki, therapeutic touch, and healing touch);[18] (6) energizing yogic breathing; and (7) others. We categorized the duration of

the intervention based upon the median duration of all interventions as < 6 weeks vs. ≥ 6 weeks.

Control groups were categorized as follows: (1) usual care or wait list control; (2) sham control (maneuver that mimics the intervention so that patients don't know their treatment assignment); (3) attention control (control that mirrors the time and attention received by those in the intervention group); (4) other mind and body practices; and (5) education.

Study Covariates

We planned to include the following study-level potential covariates: participant age (adult vs. child), cancer diagnosis (breast, colon, other single cancer type or more than one cancer type), inclusion of HSCT patients, timing of intervention (during cancer treatment including hormone therapy, following completion of treatment or both during and following treatment), exclusive enrollment of palliative care patients (as defined by each study), and presence of fatigue at baseline as an eligibility criterion for enrollment (approach to assessment and threshold varied by study) .

Risk of Bias Assessment

The Cochrane Collaboration's instrument for assessing the risk of bias in randomized trials was used.[19] Elements evaluated were adequate sequence generation, adequate allocation concealment, blinding of participants and personnel, blinding of outcome assessors and lack of attrition bias. We prioritized adequate sequence generation and adequate allocation concealment *a priori* for stratified analyses because of their potential effect on bias.[20]

Data Analysis

Data were combined at the study level and not at the individual patient level. We synthesized outcomes if there were at least three studies with outcome data within a stratum. If fatigue scores were missing summary measures, we made the following assumptions to facilitate data synthesis: the mean can be approximated by the median; the range contains six standard deviations, the 95% confidence interval (CI) contains four standard errors, and the interquartile range contains 1.35 standard deviations.[19] The severity of fatigue was synthesized using the standardized mean difference (SMD) after rescaling such that higher scores reflected more fatigue. A SMD less than 0 indicates that the mean fatigue score was lower (better) in the mind and body practice group as compared to the control group. In interpreting the SMD, 0.20 is a small effect, 0.50 is a medium effect, and 0.80 is a large effect.[21] Effects were weighted by the inverse variance and a random effects model was used for all analyses as we expected heterogeneity between the studies. Statistical heterogeneity between trials was described using the I^2 value, which reflects the percentage of total variation across studies due to heterogeneity rather than chance.[19]

The primary analysis compared all intervention groups against all control groups. Secondary analyses compared all interventions against usual care or wait list controls, and against sham controls. Sham controls were selected for subgroup analysis as they are most similar to placebo controls. Stratified analyses were then conducted that evaluated the effect of individual intervention groups against all controls and against sham controls. Sources of heterogeneity were explored using stratified analyses for the primary comparison, all interventions against all control groups, and for individual interventions which were effective in reducing fatigue.

We explored potential publication bias by visual inspection of funnel plots when at least 10 studies were available for synthesis.[19] In the event of potential publication

bias, the “trim and fill” technique was used to determine the impact of such potential bias.[22] With this technique, outlying studies are deleted and hypothetical negative studies with equal weight are created. Meta-analyses were conducted using Review Manager 5.2 (Cochrane Collaboration, Nordic Cochrane Centre).

RESULTS

Figure 1 shows the flow diagram of study identification and selection, and reasons for excluding studies. The search strategy identified 11793 unique citations, of which 617 were retrieved for full-text evaluation. Of these citations, 55 met the eligibility criteria and were included in this systematic review. There were 4975 patients included in the randomized studies. Agreement in study inclusion for the overall fatigue systematic review between the two reviewers was almost perfect ($\kappa = 0.97$, 95% CI 0.95 to 0.99).

Table 1 and Appendix C show the demographics of the included studies. The non-physical activity mind and body practices included were as follows: acupuncture or acupressure (n=12), mindfulness (n=11), relaxation techniques (n=10), massage therapy (n=6), energy therapies (n=5), energizing yogic breathing (n=3), and other interventions evaluated in one or two studies (n=8). Other interventions were hypnosis (n=2), distant therapy (n=2), meditation (n=2), and combination (n=2). We classified an intervention as energy therapy when a practitioner manipulated a patient’s energy field in person whereas distant therapy was performed from afar. Combination interventions consisted of massage plus acupressure (n=1) and meditation plus massage (n=1). In terms of control groups, 37 (67.3%) were usual care or wait list, 11 (20.0%) were sham, and 2 (3.6%) were attention controls. The two attention control studies evaluated mindfulness (n=1) and hypnosis (n=1). Almost all studies enrolled adult patients (n=52, 94.5%) and studies included breast cancer as the most common diagnostic group (n=24, 43.6%).

Table 2 and Figure 2 illustrate the effect of non-physical activity mind and body practices. When combined, all interventions significantly reduced the severity of fatigue when compared to all control groups (SMD -0.51, 95% CI -0.73 to -0.29) and when compared to usual care or wait list controls (SMD -0.59, 95% CI -0.86 to -0.31). However, when compared to sham controls, there was no significant effect of mind and body practices (SMD -0.26, 95% CI -0.68 to 0.16).

Table 3 shows the effect of specific interventions against all controls and against sham controls only. When compared to all controls, only mindfulness (SMD -0.50, $P=0.005$) and relaxation techniques (SMD -0.94, $P=0.006$) significantly reduced the severity of fatigue. Neither of these two interventions were evaluated against sham controls. In contrast, acupuncture, acupressure, massage therapy, energy therapy and energizing yogic breathing were not effective at reducing the severity of fatigue when compared to all controls (Table 3). Only acupuncture, acupressure and energy therapy were compared against sham controls and they were not effective in these analyses.

Table 4 shows the stratified analyses by study characteristics both for all interventions against all controls and individually for mindfulness and relaxation techniques against all controls. We were not able to evaluate diagnosis group because only studies of breast cancer patients had sufficient number of studies for synthesis. When evaluated both qualitatively and using the P value for interaction, the efficacy of mind and body practices together as a group as well as the efficacy of mindfulness and relaxation techniques individually were not affected by any of the evaluated study characteristics including timing of intervention, requirement of fatigue for eligibility at baseline, duration of intervention or methodological factors.

Appendix D shows the funnel plot for all interventions against all controls; no evidence of publication bias was observed.

DISCUSSION

In this systematic review, we found that as a group, non-physical activity mind and body practices significantly reduced severity of fatigue when compared to all control groups. More specifically, we found that mindfulness and relaxation were effective interventions in reducing fatigue. Acupuncture, acupressure, massage, energy therapy and yogic breathing were not effective. Study characteristics and methodological features did not influence intervention efficacy when all interventions are combined together and when mindfulness and relaxation techniques were evaluated individually.

We found that when combined into a single group, all interventions together were effective at reducing fatigue when compared to usual care or wait list controls but were not effective when compared to sham interventions. Generally, placebo or sham controls minimize the risk of reporter bias and reduce the risk that benefits are related to knowledge of treatment assignment rather than due to the effect of the intervention itself. The differential effect by usual care vs. sham controls could suggest that positive results are driven by reporter bias. However, in the stratified analyses by intervention type, we found that the interventions evaluated against sham controls (acupuncture, acupressure and energy therapy) were not effective in both the overall analysis against all control groups or in the restricted analysis against sham controls. Consequently, the finding of negative results in the sham control comparison appears to be driven, in part, by the lack of efficacy of interventions which are amenable to this type of study design.

Nevertheless, it is important to note that some sham interventions may themselves convey a therapeutic benefit and there may be a concern that sham controls are not truly effective in blinding patients to treatment or control groups. For example, Molassiotis et al[23] in a large three-arm randomized trial (acupressure vs. sham acupressure vs. usual care) comparing chemotherapy-induced nausea severity found no significant differences in nausea severity among the three study arms. However, nausea

severity was noted to be lower in the acupressure and sham acupressure arms compared to the usual care arm, suggesting a placebo effect. Furthermore, in studies of acupuncture, non-needle insertion sham controls were found to result in exaggerated treatment responses compared to needle-insertion controls.[24] In our systematic review, if patients were able to identify the difference between intervention and sham controls, we would expect to see a benefit of acupuncture in both the all control and in sham control comparisons. However, the estimates for acupuncture efficacy in these comparisons indicate that acupuncture is not effective for fatigue.

We found that mindfulness was effective at reducing fatigue severity in cancer and HSCT patients. These results are consistent with a systematic review that concluded that mindfulness was effective in women with breast cancer at improving fatigue, quality of life and sleep.[25] Other systematic reviews have suggested that mindfulness may reduce fatigue in traumatic brain injury,[26] stroke[27] and multiple sclerosis.[27] We also found that relaxation techniques were effective at improving fatigue symptoms, consistent with a review that evaluated exercise and non-pharmaceutical interventions for CRF and used indirect comparisons to conclude that relaxation was the highest ranked intervention for fatigue reduction.[28] Other systematic reviews have also suggested that relaxation techniques may reduce fatigue in osteoarthritis,[29] heart failure[30] and kidney disease.[31]

In contrast to mindfulness and relaxation which were effective at reducing fatigue, acupuncture, massage therapy and energy therapy were not effective. Mindfulness and relaxation techniques have two factors in common; they require active participation, and once learned, they can be used without assistance. These characteristics are distinct from acupuncture, massage therapy and energy therapy where individuals take on a more passive role and are reliant on a practitioner to administer therapies. By taking on a more active role in symptom management, patients

who use mindfulness and relaxation techniques may be increasing their perceived sense of self-efficacy or confidence in their personal ability to carry out a behavior that influences change in a desired direction.[32] Prior research has consistently identified self-efficacy as playing an important role in patient self-management for a variety of health conditions.[33-35]

The strengths of this review are the rigorous approach to the evaluation of non-physical activity mind and body practices for fatigue reduction and the reliance on randomized trials, which should reduce selection bias and the effect of confounding on outcomes. We also did not restrict study inclusion by language which may be particularly important when studying complementary health approaches.[36] However, there are several weaknesses of this review. First, the number of studies reduced our ability to conduct stratified analyses and diminished the power to detect subgroup differences. Second, not all studies used the same fatigue outcome which meant our analyses relied upon SMDs rather than weighted mean differences which are easier to interpret. Third, for interventions such as acupuncture which require specific expertise in administration, we could not account for practitioner variability.

In conclusion, mindfulness and relaxation were effective at reducing fatigue severity in patients with cancer and HSCT recipients. More research should be conducted that examines the mechanisms explaining the effect and identifies how programs can be structured to increase benefit. Future studies should evaluate how to translate these findings into clinical practice across different patient groups.

FUNDING

This work was supported by the Pediatric Oncology Group of Ontario. The funder did not have any influence over the content of this manuscript or the decision to submit for publication.

CONFLICT OF INTEREST STATEMENT AND DISCLOSURES

No authors declare a conflict of interest. All authors have approved the final article

References

1. Berger, A.M., et al., *Cancer-Related Fatigue, Version 2.2015*. J Natl Compr Canc Netw, 2015. **13**(8): p. 1012-39.
2. Henry, D.H., et al., *Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S.* Support Care Cancer, 2008. **16**(7): p. 791-801.
3. Hofman, M., et al., *Cancer-related fatigue: the scale of the problem*. Oncologist, 2007. **12 Suppl 1**: p. 4-10.
4. Wang, X.S., et al., *Prevalence and characteristics of moderate to severe fatigue: a multicenter study in cancer patients and survivors*. Cancer, 2014. **120**(3): p. 425-32.
5. Bower, J.E., et al., *Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life*. J Clin Oncol, 2000. **18**(4): p. 743-53.
6. Wagner, L.I. and D. Cella, *Fatigue and cancer: causes, prevalence and treatment approaches*. Br J Cancer, 2004. **91**(5): p. 822-8.
7. Tonosaki, A., *The long-term effects after hematopoietic stem cell transplant on leg muscle strength, physical inactivity and fatigue*. Eur J Oncol Nurs, 2012. **16**(5): p. 475-82.
8. Graef, D.M., et al., *Sleepiness, Fatigue, Behavioral Functioning, and Quality of Life in Survivors of Childhood Hematopoietic Stem Cell Transplant*. J Pediatr Psychol, 2016. **41**(6): p. 600-9.
9. Kim, S.H., et al., *Fatigue and depression in disease-free breast cancer survivors: prevalence, correlates, and association with quality of life*. J Pain Symptom Manage, 2008. **35**(6): p. 644-55.
10. Bower, J.E., et al., *Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation*. J Clin Oncol, 2014. **32**(17): p. 1840-50.
11. Mustian, K.M., et al., *Comparison of Pharmaceutical, Psychological, and Exercise Treatments for Cancer-Related Fatigue: A Meta-analysis*. JAMA Oncol, 2017.
12. National Center for Complementary and Integrative Health (NCCIH). 2017 [cited 2017 July 22, 2017]; Available from: <https://nccih.nih.gov>.
13. Montross-Thomas, L.P., et al., *Inpatients' Preferences, Beliefs, and Stated Willingness to Pay for Complementary and Alternative Medicine Treatments*. J Altern Complement Med, 2017. **23**(4): p. 259-263.
14. Garber, C.E., et al., *American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise*. Med Sci Sports Exerc, 2011. **43**(7): p. 1334-59.
15. Shamseer, L., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation*. BMJ, 2015. **349**: p. g7647.
16. Koch, G.G., et al., *A general methodology for the analysis of experiments with repeated measurement of categorical data*. Biometrics, 1977. **33**(1): p. 133-58.
17. Mindfulness. (n.d.). Retrieved July 22, 2017 from <https://www.merriam-webster.com/dictionary/mindfulness>, in Merriam-Webster's online dictionary.
18. Energy-therapies. (n.d.). Retrieved July 22, 2017 from <http://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/complementary-therapies/energy-therapies/?region=on>, in Canadian Cancer Society.ca.

19. Higgins, J.P.T. and S. Green, (editors), *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]* 2011. Available from www.cochrane-handbook.org.; The Cochrane Collaboration.
20. Schulz, K.F., et al., *Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials*. JAMA, 1995. **273**(5): p. 408-12.
21. Cohen, J., *Statistical Power Analysis in the Behavioral Sciences*. 2 ed 1988, Hillsdale, NJ.; Lawrence Erlbaum Associates Inc.
22. Duval, S. and R. Tweedie, *Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis*. Biometrics, 2000. **56**(2): p. 455-63.
23. Molassiotis, A., et al., *The effectiveness of acupuncture for the control and management of chemotherapy-related acute and delayed nausea: a randomized controlled trial*. J Pain Symptom Manage, 2014. **47**(1): p. 12-25.
24. Chen, H., et al., *Types of Control in Acupuncture Clinical Trials Might Affect the Conclusion of the Trials: A Review of Acupuncture on Pain Management*. J Acupunct Meridian Stud, 2016. **9**(5): p. 227-233.
25. Haller, H., et al., *Mindfulness-based interventions for women with breast cancer: an updated systematic review and meta-analysis*. Acta Oncol, 2017: p. 1-12.
26. Xu, G.Z., et al., *Complementary and alternative interventions for fatigue management after traumatic brain injury: a systematic review*. Ther Adv Neurol Disord, 2017. **10**(5): p. 229-239.
27. Ulrichsen, K.M., et al., *Clinical Utility of Mindfulness Training in the Treatment of Fatigue After Stroke, Traumatic Brain Injury and Multiple Sclerosis: A Systematic Literature Review and Meta-analysis*. Front Psychol, 2016. **7**: p. 912.
28. Hilfiker, R., et al., *Exercise and other non-pharmaceutical interventions for cancer-related fatigue in patients during or after cancer treatment: a systematic review incorporating an indirect-comparisons meta-analysis*. Br J Sports Med, 2017.
29. Zhang, L., et al., *Effects of psychological interventions for patients with osteoarthritis: a systematic review and meta-analysis*. Psychol Health Med, 2017: p. 1-17.
30. Kwekkeboom, K.L. and L.C. Bratzke, *A Systematic Review of Relaxation, Meditation, and Guided Imagery Strategies for Symptom Management in Heart Failure*. J Cardiovasc Nurs, 2016. **31**(5): p. 457-68.
31. Picariello, F., et al., *Examining the efficacy of social-psychological interventions for the management of fatigue in end-stage kidney disease (ESKD): a systematic review with meta-analysis*. Health Psychol Rev, 2017. **11**(2): p. 197-216.
32. Bandura, A., *Self-efficacy: toward a unifying theory of behavioral change*. Psychol Rev, 1977. **84**(2): p. 191-215.
33. Bodenheimer, T., et al., *Patient self-management of chronic disease in primary care*. JAMA, 2002. **288**(19): p. 2469-75.
34. Ritter, P.L., J. Lee, and K. Lorig, *Moderators of chronic disease self-management programs: who benefits?* Chronic Illn, 2011. **7**(2): p. 162-72.
35. Marks, R., J.P. Algrante, and K. Lorig, *A review and synthesis of research evidence for self-efficacy-enhancing interventions for reducing chronic disability: implications for health education practice (part I)*. Health Promot Pract, 2005. **6**(1): p. 37-43.
36. Pham, B., et al., *Language of publication restrictions in systematic reviews gave different results depending on whether the intervention was conventional or complementary*. J Clin Epidemiol, 2005. **58**(8): p. 769-76.

Table 1: Characteristics of Included Studies in the Systematic Review (N=55)

Characteristic	No. of Studies (%)
Study Population	
Participant Age	
Adults	52 (94.5)
Children	3 (5.5)
Cancer Diagnosis	
Breast	24 (43.6)
Colon	3 (5.5)
Other cancer types*	4 (7.3)
More than one cancer	24 (43.6)
Hematopoietic Stem Cell Transplant Recipients	4 (7.3)
Timing of Intervention	
During cancer treatment	32 (58.2)
Following completion of treatment	8 (14.5)
Both during and following treatment	11 (20.0)
Unknown	4 (7.3)
Palliative Care Setting Only	2 (3.6)
Required Fatigue for Eligibility	22 (40.0)
Intervention and Control Group	
Intervention Type	
Acupuncture and acupressure	12 (21.8)
Acupuncture	6
Acupressure	6
Mindfulness	11 (20.0)
Relaxation techniques	10 (18.2)
Massage therapy	6 (10.9)
Energy therapy	5 (9.1)
Energizing yogic breathing	3 (5.5)
Other**	8 (14.5)
Duration of Intervention*	
< 6 weeks	23 (41.8)
≥ 6 weeks	28 (50.9)
Unknown	4 (7.3)
Control Group Type	
Usual care or wait list	37 (67.3)
Sham intervention	11 (20.0)
Attention control	2 (3.6)
Other mind body practices	3 (5.5)
Education	2 (3.6)
Low Risk of Bias	
Adequate sequence generation	28 (50.9)
Adequate allocation concealment	20 (36.4)
Participants and personnel blinded	0 (0)
Outcome assessors blinded	14 (25.5)
Lack of attrition bias	42 (76.4)

Free of selective reporting	52 (94.5)
-----------------------------	-----------

* Other cancers were lung (n=2) and leukemia (n=2)

** Other included hypnosis (n=2), distant therapy (n=2), meditation (n=2), and combination (n=2; massage plus acupressure and meditation plus massage)

Table 2: Mind and Body Practice on Fatigue Stratified by Control Group Type

Outcome	No. of Studies	No. of Patients	SMD*	95% CI	I² (%)	P Value
All Interventions vs. All Controls	37	2808	-0.51	-0.73, -0.29	86%	<0.00001
All Interventions vs. Usual Care or Wait List Controls	25	2152	-0.59	-0.86, -0.31	88%	<0.0001
All Interventions vs. Sham Interventions	9	456	-0.26	-0.68, 0.16	77%	0.22

Abbreviations: SMD - standardized mean difference; CI – confidence interval

*A SMD less than 0 indicates that the mean fatigue score was lower (better) as compared to the control group. SMD 0.20 is a small effect, 0.50 is a medium effect, and 0.80 is a large effect.

Table 3: Effect of Mind and Body Practices on Fatigue by Intervention Type and Control Group

Outcome	No. of Studies	No. of Patients	SMD	95% CI	I ² (%)	P Value
Interventions vs. All Controls						
Acupuncture and acupressure	7	462	-0.40	-0.86, 0.05	79%	0.08
Acupuncture	3	119	-0.13	-0.65, 0.39	40%	0.63
Acupressure	4	343	-0.60	-1.28, 0.09	87%	0.09
Mindfulness	7	807	-0.50	-0.85, -0.15	77%	0.005
Relaxation techniques	8	682	-0.94	-1.61, -0.27	93%	0.006
Massage therapy			NSP			
Energy therapy	5	189	0.08	-0.64, 0.80	82%	0.83
Energizing yogic breathing	3	201	-0.48	-1.06, 0.10	54%	0.10
Interventions vs. Sham Controls						
Acupuncture and acupressure	6	304	-0.30	-0.77, 0.16	71%	0.20
Acupuncture	3	119	-0.13	-0.65, 0.39	40%	0.63
Acupressure	3	185	-0.53	-1.45, 0.40	85%	0.26
Mindfulness			NSP			
Relaxation techniques			NSP			
Massage therapy			NSP			
Energy therapy	3	152	-0.14	-1.13, 0.85	89%	0.78
Energizing yogic breathing			NSP			

Abbreviations: SMD - standardized mean difference; CI – confidence interval; NSP – no synthesis possible because too few studies with outcome data

Table 4: Effect of Mind Body Practices vs all Control Groups on Fatigue Stratified by Study Characteristics

Subgroup	No. of Studies	No. of Patients	SMD	95% CI	I ²	P Values
Interventions vs. All Controls						
Timing of Intervention						<i>Pint = 0.82</i>
During cancer treatment	22	1502	-0.50	-0.85, -0.16	89%	0.004
Following completion of treatment	6	304	-0.51	-0.82, -0.20	34%	0.001
Both during and following treatment	6	833	-0.39	-0.66, -0.12	68%	0.005
Required Fatigue for Eligibility						<i>Pint = 0.42</i>
Yes	15	930	-0.62	-1.08, -0.17	89%	0.007
No	22	1878	-0.42	-0.65, -0.20	80%	0.0002
Duration of Intervention						<i>Pint = 0.78</i>
< 6 weeks	13	736	-0.44	-1.00, 0.12	91%	0.12
≥ 6 weeks	21	1786	-0.52	-0.75, -0.30	79%	<0.00001
Adequate Sequence Generation						<i>Pint = 0.91</i>
Yes	20	1775	-0.50	-0.81, -0.18	89%	0.002
No	17	1033	-0.51	-0.82, -0.21	80%	0.0009
Adequate Allocation Concealment						<i>Pint = 0.47</i>
Yes	16	1201	-0.41	-0.79, -0.03	89%	0.04
No	21	1617	-0.58	-0.85, -0.31	83%	<0.00001
Mindfulness vs. All Controls						
Timing of Intervention						<i>Pint = 0.34</i>
Following completion of treatment	3	201	-0.47	-0.80, -0.14	15%	0.005
Both during and following treatment	3	582	-0.26	-0.53, -0.00	54%	0.05
Required Fatigue for Eligibility						<i>Pint = 0.09</i>
Yes	3	176	-1.15	-2.15, -0.15	87%	0.02
No	4	631	-0.26	-0.48, -0.03	40%	0.03
Duration of Intervention			NSP			
Adequate Sequence Generation						<i>Pint = 0.33</i>
Yes	4	665	-0.36	-0.63, -0.08	62%	0.01
No	3	142	-1.01	-2.29, 0.28	88%	0.12
Adequate Allocation Concealment			NSP			

Relaxation Techniques vs. All Controls						
Timing of Intervention			NSP			
Required Fatigue for Eligibility			NSP			
Duration of Intervention						<i>Pint = 0.93</i>
< 6 weeks	3	354	-1.08	-2.38, 0.22	96%	0.10
≥ 6 weeks	4	265	-1.14	-1.71, -0.58	74%	<0.0001
Adequate Sequence Generation						<i>Pint = 0.22</i>
Yes	4	389	-1.34	-2.43, -0.25	95%	0.02
No	4	293	-0.54	-1.22, 0.14	86%	0.12
Adequate Allocation Concealment						<i>Pint = 0.75</i>
Yes	3	354	-1.08	-2.38, 0.22	96%	0.10
No	5	328	-0.84	-1.57, -0.11	89%	0.02

Abbreviations: SMD – standardized mean difference; CI – confidence interval; Pint – P value for interaction; NSP – no synthesis possible since not enough studies available for at least two strata

Figure 1 Legend: Flow diagram Depicting Study Identification, Selection and Reasons for Exclusion

Figure 2 Legend: Forest Plot of Mind Body Practices vs. Controls Stratified by

Intervention Type

Forest plot of studies comparing mind and body practices versus controls for fatigue reduction.

Squares to the left of the vertical line mean that the intervention is better than control. Horizontal

lines through the squares represent 95% confidence intervals (CIs). The size of the squares

reflects each study's relative weight, and the diamond represents the aggregate standardized

mean difference (SMD) and 95% CI.

Figure 1: Flow diagram Depicting Study Identification, Selection and Reasons for Exclusion

Figure 2: Forest Plot of Mind Body Practices vs. Controls Stratified by Intervention Type