Internet-Based Mindfulness Interventions to Improve Wellbeing and Mental Health in Cancer Patients: A Systematic Review

Shotaro Asano

Supervisor: Katharina da Silva Lopes, MSc, MPH, PhD

St. Luke's International University
Graduate School of Public Health

Capstone Project

2020/21

Table of Contents

Abstract

Background

Cancer patients are known as high-risk populations for mental disorder complications, and one in three patients experience psychological distress. For this reason mindfulness based interventions (MBIs) are increasingly used to support cancer patients. MBIs are expected to improve mood and quality of life of patients by reducing depressive symptoms, anxiety, and other emotional distress. Internet-based mindfulness interventions (eMBIs) offer MBI via online settings, which are reported to be equally effective compared with MBIs. However, eMBIs application specifically for cancer patients have not been reviewed to date.

Objectives

This study aimed to conduct a systematic review of the potential benefits of eMBI for cancer patients.

Methods

We conducted an extensive search of databases and registries (PubMed, The Cochrane library, PsycINFO, Science Direct, CINAHL and EMBASE), using Medical Subject Headings (MeSH) terms and keywords. All papers published before September 5th. 2020 were included. No language restrictions were applied. Only trial studies, which met the inclusion criteria were selected. Two reviewers independently selected studies, assessed risks of bias using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), and one reviewer extracted data from all included studies.

Main Results

Of the identified 2361 records from all databases, we included seven randomized controlled trials (RCT) in the qualitative synthesis. The studies ranged in size from 11 eMBI participants to 104 eMBI participants from North America, Europe and Australia and were published between 2014 and 2020. The most common cancer type among the studies was breast cancer.

Three studies focused on anxiety and all reported the eMBI group had significant positive effect over control groups. Three studies focused on psychological distress and two of them reported eMBIs were effective. Two out of five studies reported the effectiveness of eMBI on quality of life. One study focused depression reporting that eMBI was effective at post-intervention, but not for follow-up period. Three studies focused on perceived stress but only study reported the effectiveness of eMBI.

Conclusions

We found that the use of eMBIs for cancer patients may have a positive effect on anxiety symptoms but uncertain positive results for psychological distress and depression. There may be little to no effect for QOL and perceived stress. Future studies should focus on simpler delivery modes such as app-based interventions as well as using popularly used measurement scales. Furthermore, future studies should also be conducted in Asia, Middle East and Africa.

Background

Every year more than 18 million people are newly diagnosed with some type of cancer (Ferlay et al., 2019). Cancer patients are known as high-risk populations for mental disorder complications, and one in three patients experience psychological distress (Carlson et al., 2004). In Scotland, United Kingdom, the prevalence of depression, by cancer type, has been reported to be the highest among patients with lung cancer (13.1%, 95% CI: 11.9 –14.2%), followed by gynecological cancer (10.9%, 95% CI: 9.8 – 12.1), breast cancer (9.3%, 95% CI: 8.7 – 10.0), colorectal cancer (7·0%, 95% CI: 6.1 –8.0), and genitourinary cancer (5·6%, 95% CI: 4.5 – 6.7) (Walker et al., 2014).

Mindfulness based interventions (MBIs) are increasingly used to support cancer patients (Kabat-Zinn, 2013). Mindfulness is a kind of meditation technique, which involves moment-to-moment nonjudgmental awareness (Shapiro et al., 2006). MBIs are expected to improve mood and quality of life of the patients by reducing depressive symptoms, anxiety, and other emotional distress.

MBI offered via online settings (eMBIs), have been reported to be equally effective compared with MBIs (Compen et al., 2017). However, eMBIs for cancer patients have not been specifically reviewed to date. Two existing systematic reviews addressed a broader population including cancer patients (Russell et al., 2018; Toivonen et al., 2017). The systematic reviews did not primarily focus on eMBIs and cancer patients, but included two to three studies with cancer patients. Since the reviews were conducted, several new quantitative studies have been published regarding cancer patients, making it necessary to update the evidence base for this population. This review will help to examine the effectiveness as well as the limitation of eMBIs for cancer patients.

Importance of this Review

The development of early detection and treatment for cancer had evolved remarkably over the decades leading to greater chances of surviving cancer and also a longer time living with cancer. This consequently leads to a potential increase of mental health issues in cancer patients and survivors. The application of eMBIs for cancer patients is one of the new approaches for addressing their mental health issues. Despite the fact that many studies over the last decade have examined the potential benefits of eMBIs for cancer patients, there is a lack of definitive evidence as to whether or not eMBIs are effective.

Aim and Objectives

The aim of this study was to assess the effectiveness and limitations of eMBIs to improve mood and quality of life of cancer patients. The objectives were to: a) quantitatively evaluate effectiveness of eMBIs for cancer patients and survivors; b) provide a description of characteristics of studies in terms of study design, region, and population, and c) examine the most effective form of eMBIs (mode of delivery, number of sessions, estimated time used for intervention, duration, and etc.).

Methods

Criteria for Considering Studies for this Review

Since the objective of this systematic review was to evaluate effectiveness of eMBI for cancer patients and survivors, the inclusion criteria were studies examining individuals with cancer diagnosis that received a eMBI intervention. As for population,

all patients 18 years or older, in any place/setting, who were diagnosed with any type of cancer, at any stage including survivors were included. Patients were excluded if they already had a mental disorder diagnosis before the diagnosis of cancer.

In this review, eMBI is defined as an intervention delivered or accessed via the internet with 100% of interactions done online and offering MBI or any mindfulness-based activities (Compen, 2018). The following exclusions were made to measure the benefit of mindfulness separate from confounding elements: (a) co-intervention with other methods including face-to-face MBI session; (b) interventions, which included a component of mindfulness but did not emphasize it, or therapies containing elements of mindfulness practice; and (c) couple-based intervention where eMBI was delivered to cancer patients and spouses together.

Comparisons considered included usual care, any alternative interventions, wait-list, or as defined by trialists. In this study, outcomes were defined as psychological distress, including depression, anxiety, fear of cancer recurrence, post-traumatic stress, and perceived stress in cancer patients and survivors.

Only randomized controlled trials (RCTs), quasi-RCTs, and cluster RCTs were eligible for inclusion. Excluded were observational studies, abstracts of RCTs (e.g., from conferences), cross-sectional studies, case reports, review articles, dissertations, and commentaries. These exclusions were made to measure the effectiveness of mindfulness.

Table 1

Summarized Eligibility Criteria in PICO Format

	Inclusion	Exclusion
Population	- Age: 18 years or older - Health condition: diagnosed with any type cancer - Cancer stage: any stage including survivors - Place: both in hospital and home	If patients suffered solely (before diagnosis of cancer) from mental disorders or addiction or substance abuse defined in ICD-10 diagnosis codes F01– F99
Interventions	eMBIs meeting the following standards: 1) delivered or accessed via the internet with 100% of interactions done online 2) offering mindfulness-based activities such as mindfulness meditations and informal mindfulness practices	- Co-intervention with other methods including face to face MBI session - Intervention, which included a component of mindfulness but did not emphasize it (e.g., multi-week programs with mindfulness practice delivered only in one or two sessions) or therapies contained elements of mindfulness practice (e.g., acceptance and commitment therapy, cognitive behavioral therapy, Yoga, Tai-chi) - Couple-based intervention where eMBI was delivered to cancer patient and spouse together were excluded.
Comparison	Comparison could be groups of usual care, any alternative interventions, wait-list, or as defined by trialists	
Outcome	- QOL, psychological distress including anxiety, fear of cancer recurrence, depression and perceived stress in cancer patients and survivors - Measurement: All the quantitative assessments with validated scales used by trialists including General Health Questionnaire-28, WHOQOL, MAX-PC, SF-8, STAI, CESD, SF-36, EPIC-26, HADS, and similar..	
Study Type	Randomized controlled trials (RCT) including cluster RCTs and quasi RCTs	Observational studies, abstracts of RCTs (e.g., from conferences), cross-sectional studies, case reports, review articles, dissertations, and commentaries

Note: PICO = population, intervention, comparison, outcome; ICD = international classification of disease; eMBIs = internet mindfulness based interventions; MBI = mindfulness based intervention; QoL = quality of life; WHOQOL= The World Health Organization Quality of Life; MAX-PC = Memorial Anxiety Scale for Prostate Cancer; SF-8 = Short-Form Health Survey; STAI = Spielberger State-Trait Anxiety Inventory ; CESD = Center for Epidemiological Studies Depression ; SF-36 = Short-Form Health Survey; EPIC-26 = Expanded Prostate Cancer Index Composite; HADS = Hospital Anxiety and Depression Scale

Search Methods for Identification of Studies

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISMA) (Moher et al., 2009). A literature search was conducted in the following databases on 5 September 2020:

- PubMed
- The Cochrane library
- PsycINFO
- Science Direct
- CINAHL
- EMBASE

All searches included Medical Subject Headings (MeSH) terms and keywords which were combined with the Boolean operators AND and OR. Search terms were initially set in PubMed and deployed to other databases. All papers published before September 5th. 2020 were included. No language restrictions were applied. After identifying records, duplicates were initially removed in the citation management software Zotero, and again in the systematic review web software Rayyan QCRI (Ouzzani, 2016). The search strategies are shown in the Appendix B.

Study Selection

Titles and abstracts of identified records were independently screened by two reviewers on Rayyan. References not meeting eligibility criteria were excluded. Disagreements were resolved by consensus through discussion among the reviewers. Then, two reviewers independently screened the full-texts and disagreements were

resolved by discussion. The study selection process is summarized in the PRISMA flow diagram in Figure 1.

Data Extraction

I created a data table for study characteristics and outcome data, which we pilot tested. Then, one reviewer extracted the following items:

- Study information: first author, year, country, study design
- Population: sample characteristics, cancer type, time points since diagnosis, mean age in years, percentage of female
- Intervention: mode of delivery, duration, number of sessions
- Comparison
- Outcome: measurements, results (effect size, and p-value; when studies do not report effect size, between group mean difference is extracted in replacement)

Risk of Bias Assessment

The methodological quality of included studies was assessed by criteria defined in in the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (Sterne et al., 2019). Two reviewers independently assessed risk of bias. Disagreements were resolved by consensus through discussion. The assessment was done for five domains, namely "risk of bias arising from the randomization process", "risk of bias due to deviations from the intended interventions (effect of assignment to intervention)", "missing outcome data", "risk of bias in measurement of the outcome", and "risk of bias in selection of the reported result".

In this review, because examining the effectiveness of the intervention was important, we selected the following three domains as the most important ones: “risk of bias arising from the randomization process”; “risk of bias due to deviations from the intended interventions (effect of assignment to intervention)”, and “risk of bias in measurement of the outcome”. Overall judgement was rated and processed as follows: ‘high risk’ and ‘some concerns’ from important domains were counted as 1 point; points from the five domains were summed. Four to 5 points indicated the study was of overall ‘high risk’; 2 to 3 points ‘some concerns’; 0 to 1 point ‘low risk’.

Results

Description of Studies

Results of the Search

I identified a total of 2,361 records the database search. Records from each database were CENTRAL (n = 1,124), EMBASE (n = 398), MEDLINE (n = 588), CINAHL (n = 233) and Psycho INFO (n = 18).

After duplicate removal, two reviewers screened 1,380 titles and abstracts and excluded 1,350 irrelevant records. Full-text analysis was done to the remaining 30 records. After reading the full texts, two reviewers excluded 23 studies due to not meeting the eligibility criteria. Reasons for exclusion are shown in Figure 1. Finally, I included seven studies in the qualitative synthesis.

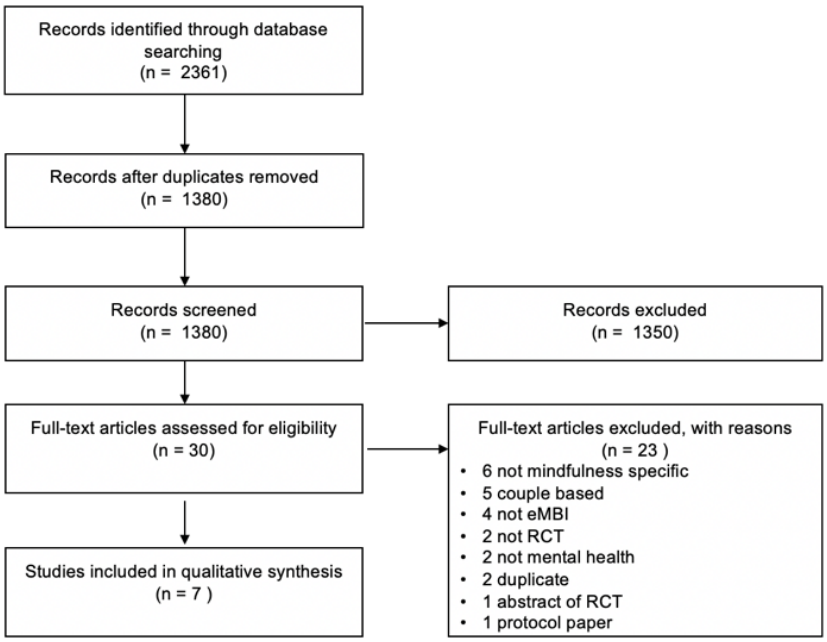

Figure 1

PRISMA Flow Diagram

Summary of Included Studies

I included seven full-text peer-reviewed studies of eMBI interventions (see Table 2). The studies were published between 2014 (Zernicke 2014) and 2020 (Nissen, 2020). Two studies originated from The Netherlands (Bruggeman-Everts 2017; Compen 2018), two from USA (Messer 2019; Rosen 2018), one each from Australia (Russell 2018), Canada (Zernicke 2014) and Denmark (Nissen 2020). All studies were RCTs, including two 3-arm RCTs (Bruggeman-Everts 2017; Compen 2018).

As for participants, three studies included both patients and survivors (Compen 2018; Rosen 2018; Zernicke 2014), and four studies included only survivors. The studies ranged in size from 11 eMBI participants (Messer 2019) to 104 eMBI participants (Nissen 2020). Five studies included multiple cancer types (Bruggeman-

Everts 2017; Compen 2018; Messer 2019; Nissen 2020; Zernicke 2014). The most common cancer type among the studies was breast cancer; in four studies 45% of the patients were breast cancer patients (Bruggeman-Everts 2017; Compen 2018; Nissen 2020; Zernicke 2014). There were two "single cancer type" studies; one included only breast cancer patients (Rosen 2018) and the other included only patients with melanoma (Russel 2018). The mean age of participants ranged from 51.36（Bruggeman-Everts 2017) to 58 years (Zernicke 2014), and the mean percentage of females ranged from 54% (Russell 2018) to 100% (Rosen 2018).

The most common mode of delivery was a series of 6 to 9, 1-week module sessions offered in five studies (Bruggeman-Everts 2017; Compen 2018; Messer 2019; Nissen 2020; Russel 2018). The module included pre-recorded video, audio file, text reading materials, or a combination of all. Of the five studies, four (Bruggeman-Everts 2017; Compen 2018; Messer 2019; Nissen 2020) had a therapist involved who gave email feedback to participants' writing tasks, and one study (Russel 2018) did not involve a therapist. As alternatives, one study used a commercially available "app" (Rosen 2018), and another study delivered eMBI as a synchronous virtual classroom (Zernicke 2014). The studies ranged in duration from 6 weeks to 9 weeks. The estimated time of the intervention ranged from 4 minutes (Russel 2018) to 4 hours (Bruggeman-Everts 2017) per session.

As for comparison, face-to-face MBI was examined in only one study (Compen 2018), and alternative interventions, which were ambulant activity feedback therapy (AAF) and psycho-educational emails, also were examined in only one study (Bruggeman-Everts 2017). For the remaining studies, one study had "treatment as

usual" as a comparison (Messer 2019), and four had waitlists as comparisons (Nissen 2020; Rosen 2018; Russel 2018; Zernicke 2014).

The most frequently used tools for each outcome measure were: for QOL, Profile of Mood States (POMS) (Searight & Montone, 2017); for psychological distress, Hospital Anxiety and Depression Scale (HADS) (Spinhoven et al., 1997); for anxiety including Fear of Cancer Recurrence" (FCRI) (van Helmondt et al., 2017)) for depression, Beck Depression Inventory (BDI-II) (Upton, 2013); and for perceived stress, Perceived Stress Scale 10 (PSS-10) (Cohen & Williamson, 1988).

Table 2

PICO Study Characteristics by Included Studies

Study information	Population			Intervention			Comparison	Outcome
First Author, Year, Country, Study Design	Sample characteristics, time points	Participant cancer type	Mean age in years (SD), % of female	Mode of delivery	Mindfulness Activities	Number of sessions, estimated time used for intervention, duration	Comparison group, mean age in years	Outcome measures (tool)
Bruggeman-Everts, 2017 Netherlands RCT (3-arm)	Cancer survivors All (n=167) eMBI (n=55) Time points: 3 months since remission	**Multiple** -Breast 45% -Reproductive organs 15% -Blood, bone marrow, Hodgkin's 13% -Others 27%	Age: 51.36 (12.04) % of female: 71%	- Web-based psychologist-guided intervention, which follows the MBCT protocol specifically designed for CCRF - Therapists involved	- 1-week modules with reading material, audio exercises, and writing tasks - Receiving feedback from therapists in weekly basis - Replying to this feedback by email	9 weekly sessions, 4 hours per session (on average) Duration: 9 weeks	AAF (n=62) Age: 56.45 (9.25) PE (n=50) Age: 56.54 (8.43)	Psychological Distress (HADS)
Compen, 2018 Netherlands RCT (3-arm)	Cancer patients and survivors All (n=245) eMBI (n=90) Time points: any time after diagnosis	**Multiple** -Breast 59% -Gynecologic 10% -Prostate 8% -Others 23%	Age: 51.7 (10.7) % of female: 86%	- Pre-recorded videos by MBSR teacher delivered individually via online - Therapists involved	- 1-week modules with reading material, video exercises, writing tasks, - Receiving feedback from therapists after week 5 for silent day at home. -After the feedback, practicing a silent day and write their experiences in an essay	8 weekly sessions, 2.5 hours per session Duration: 8 weeks	MBI (n=77) Age: 52.1 (11.4) TAU (n=78) Age: 50.4 (9.9)	- QOL (SF-12 Mental, SF-12 Physical) - Psychological Distress (HADS) - Fear of Cancer Recurrence (FCRI)
Messer, 2019 U.S.A. RCT	Cancer survivors All (n=21) eMBI (n=11) Time points: 3years since remission	**Multiple** -details not reported	Age: n/a % of female: 67%	- Six guided meditation audio clips and brief textual lessons - Therapists involved	1-week modules with reading material, audio exercises, writing tasks	6 weekly sessions, 8 to 17 minutes per session Duration: 6 weeks	TAU (n=10) Age: n/a	- QOL (POMS-SF) - Psychological Distress (HADS)
Nissen, 2020 Denmark RCT	Cancer survivors All (n=150 eMBI (n=104) Time points: more than 3 months and less than 5 years since remission	**Multiple** -Breast 92% -Prostate 8%	Age: n/a % of female: n/a	- Combination of text reading, audio files, writing tasks, and videos - Therapists involved	- 1-week modules with reading material, audio exercises, writing tasks, cancer-specific patient examples, and videos with patients and experts - Completed and shared with therapist a weekly training diary and receive written, asynchronous feedback	8 weekly sessions, estimated time used is not reported Duration: 8 weeks	waitlist (n=46) Age: n/a	- QOL(WHO-5) - Anxiety (STAI-Y) - Depression (BDI-II) - Perceived Stress (PSS-10)
Rosen, 2018 U.S.A. RCT	Cancer patients and survivors All (n=112) eMBI (n=57) Time points: anytime less than or equal to 5 years after diagnosis	Breast	Age: 51.40(10.73) % of female: 100%	Commercially available mindfulness app (Headspace)	- Headspace content is a mix of audio and animated video - Beginning with a 10-day foundation course (Take10 program) - After completing the Take10 program, participants gained access to additional training courses focused on areas such as sleep or stress	Participant interaction with the app was self-guided to approximate typical day-to-day use and estimated time used is not reported Duration: 8 weeks	waitlist (n=55) Age: 53.22(9.91)	QOL (FACT-B)

Table 2 (continued)

PICO Study Characteristics by Included Studies

Study information	Population			Intervention			Comparison	Outcome
First Author, Year, Country, Study Design	Sample characteristics, time points	Participant cancer type	Mean age in years (SD), % of female	Mode of delivery	Mindfulness Activities	Number of sessions, estimated time used for intervention, duration	Comparison group, mean age in years	Outcome measures (tool)
Russell, 2018 Australia RCT	Cancer survivors All (n=69) eMBI (n=46) Time points: anytime less than or equal to 5 years since remission	Melanoma	Age: 53.5(12.1) % of female: 54%	Combination of text reading, audio files, writing tasks, and videos	1-week modules with reading material, audio exercises, writing tasks	6 weekly sessions, and ranged 4 - 260 min per session Duration: 6 weeks	waitlist (n=23) Age: 53.1(15.2)	-Fear of Cancer Recurrence (FCRI) - Perceived Stress (PSS-10)
Zernicke, 2014 Canada RCT	Cancer patients and survivors All (n=62) eMBI(n=32) Time points: within the last 3 years since remission	**Multiple** -Breast 47% -Colon/Gastrointestinal 17% -Thyroid 10% -Others 26%	Age: 58 (8.2) % of female: 73%	Synchronous online virtual classroom session with recordings and videos for additional home practice	Detail not provided (mentioned that it is based on Mindfulness-based Cancer Recovery program)	8 weekly sessions, 2 hours per session Duration: 8 weeks	waitlist (n=30) Age: 58 (13.0)	- QOL (POMS) - Perceived Stress (CSOSI)

PICO = population, intervention, comparison, outcome; eMBI = Internet-based mindfulness-based intervention; MBCT = Mindfulness-based cognitive therapy; CCRF = Chronic cancer-related fatigue; AAF = Ambulant activity feedback therapy; PE = Psycho-educational emails; HADS = Hospital anxiety and depression scale; MBSR = Mindfulness-based stress reduction; TAU = Treatment as usual; SF-12 Mental, SF-12 Physical = Mental and physical scales of the short-form 12; FCRI = Fear of cancer recurrence inventory; QOL = Quality of life; POMS-SF = Profile of mood states short form; WHO-5 = The World Health Organization - five well-being index; STAI-Y = State-trait anxiety inventory Y-form; BDI-II = Beck depression inventory; PSS-10 = Perceived stress scale 10; FACT-B = Functional assessment of cancer therapy - breast version 4; CSOSI = Calgary symptoms of stress inventory; n/a = not available

Risk of Bias in Included Studies

For overall risk of bias, we judged one study as ‘low risk’ and the remaining either ‘high risk’ or ‘some concerns’ due to our rating and process. Figure 2 depicts a graph of ‘risk of bias’ and Figure 3 is a summary of ‘risk of bias’ assessment based on the RoB 2 tool (Sterne et al., 2019). The ‘risk of bias’ results for each of the included studies in five domains are provided with reasons and comments for judgements in Appendix A.

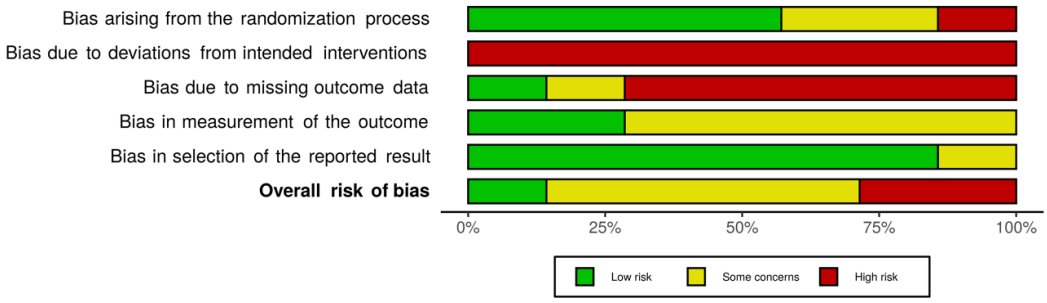

Figure 2

Risk of Bias Graph

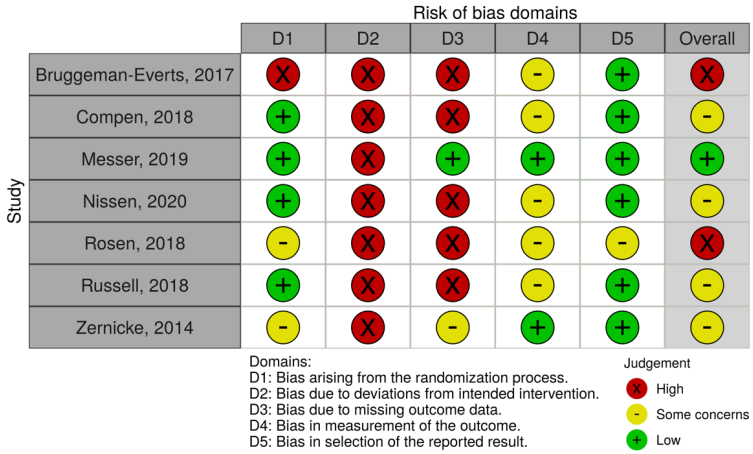

Figure 3

Risk of Bias Summary

Risk of Bias Arising from the Randomization Process

Two reviewers assessed most of the studies as low risk of bias. For one study (Bruggeman-Everts 2017), the baseline HADS were different among groups, and also authors reported that there was algorithm error of randomization. For two studies with concerns (Rosen 2018; Zernicke 2014), both seemed to have a robust process for randomization. However, one study (Rosen 2018) had higher health literacy and education levels in the intervention group, which potentially affected the outcome, and the other (Zernicke 2014) allocation of cancer type was significantly different by having twice as many breast cancer patients included in the intervention group than for the control group.

Risk of Bias Due to Deviations from the Intended Interventions (Effect of Assignment to Intervention)

Two reviewers assessed all of the studies as high risk of bias due to lack of blinding of the intervention in both patients and researchers/medical staff. Most studies mentioned this limitation of non-blinding due to the nature of eMBI.

Missing Outcome Data

Two reviewers assessed five studies (Bruggeman-Everts 2017; Compen 2018; Nissen 2020; Rosen 2018; Russell 2018) as high risk of bias due to the high rate of dropouts (> 20%). In all studies, the intervention group had a higher dropout rate than the control group. Potential reasons of dropouts were high intensity of the program compared to control groups, or poor usability of the online tools. Also, it was possible

that only participants interested in meditation actually completed the studies. This could potentially have affected the outcome of the study.

Risk of Bias in Measurement of the Outcome

With regards to the previous domain, the five studies (Bruggeman-Everts 2017; Compen 2018; Nissen 2020; Rosen 2018; Russell 2018) had concerns about having completers who were possibly more interested in eMBIs and thus responded to questionnaires compared with dropouts.

Risk of Bias in Selection of the Reported Result

Six studies were assessed as low risk of bias for this domain (Bruggeman-Everts 2017; Compen 2018; Messer 2019; Nissen 2020; Russell 2018; Zernicke 2014). We did not find any particular problems in their process and results. One study (Rosen 2018) was rated as some concerns due to lack of information.

Effects of Interventions

A summary of results for eMBIs compared with controls is presented in Table 3. For the outcome specific columns, results for each outcome measures are stated with effect size (Cohen's d) and p-value extracted from each study. When studies did not report the effect size, between group mean difference was extracted instead.

Quality of Life

Five studies reported on this outcome (Compen 2018; Messer 2019; Nissen 2020; Rosen 2018; Zernicke 2014). Three studies (Messer 2019; Rosen 2018; Zernicke 2014) reported that the eMBI group had a significant effect over the control group. However, one study reported the eMBI intervention was not effective (Nissen 2020), and another reported the effectiveness for only the mental scale and not for the physical scale (Compen 2018).

Psychological Distress

Three studies reported this outcome (Bruggeman-Everts 2017; Compen 2018; Messer 2019) but one study (Bruggeman-Everts 2017) did not provide data because it had a different primary outcome and psychological distress was not its focus. However the two studies (Compen 2018; Messer 2019), reported the use of eMBIs as effective to reduce psychological distress.

Anxiety

Three studies reported this outcome (Compen 2018; Nissen 2020; Russell 2018) and all reported that the eMBI group had significant positive effects over the control

groups. This result suggests that eMBI may have a robust, durable effect on anxiety symptoms in cancer patients and survivors.

Depression

One study included this outcome. Nissen, et al. (2020), reported that the eMBI group had a significant positive effect over the control group at post-intervention, but not for the follow-up period. A potential reason for this result mentioned by the authors was the baseline scores were within the range of "mild depression," which could indicate a floor effect.

Perceived Stress

Three studies included this outcome (Nissen 2020; Russell 2018; Zernicke 2014) and two studies (Nissen 2020; Russell 2018) reported the eMBI group did not have a significant effect over the control group. One study (Zernicke 2014) reported it reduced perceived stress, but it used a different measurement scale (CSOSI) and thus making comparisons unusable.

Table 3

Su*mmary of Studies by Results*

Study	Intervention	Effectiveness and effects	Outcome specific					Risk of Bias
			QOL	Psychological Distress	Anxiety	Depression	Perceived Stress	
Bruggeman-Everts, 2017	Web-based psychologist-guided intervention, which follows the MBCT protocol specifically designed for CCRF.	Details not reported for psychological distress	n/a	Details not reported	n/a	n/a	n/a	High risk
Compen, 2018	Pre-recorded videos by MBSR teacher delivered individually via online (no application [app] required)	Significant effects in all measures over TAU except for QOL (physical) Proportion of patients improved is significantly greater in eMBI than TAU	Mental: - Effective (d = 0.67, p <0.001) Physical: - Not Effective (d = 0.24, p <0.21)	Effective (d = 0.71, p <0.001)	Effective (d = 0.53, p <0.001)	n/a	n/a	Some Concerns
Messer, 2019	Six guided meditation audio clips and brief textual lessons	Significant effects for both psychological distress and QOL	Effective (Between group mean difference = -20.6, p = .044)	Effective (Between group mean difference = -6.87, p = .014)	n/a	n/a	n/a	Low Risk
Nissen, 2020	Combination of text reading, audio files, writing tasks, and videos	Significant effects for anxiety and depression, but the effects were not maintained at follow-up for depression No group difference was found for QOL and perceived stress	Not effective (d = 0.25, p= .173)	n/a	Effective both at post-intervention (d = 0.45, p = .017) and follow-up (d = 0.40, p = .029)	Effective at post-intervention (d = 0.42, p = .024) but not follow-up (d = 0.28, p = .131)	Not effective (d = 0.18, p = .331)	Some Concerns
Rosen, 2018	Commercially available mindfulness app (Headspace)	Significant effect for QOL over controls	Effective (d = 0.31, p <0.01)	n/a	n/a	n/a	n/a	High risk
Russell, 2018	Combination of text reading, audio files, writing tasks, and videos	Significant effect for the severity of "fear of cancer recurrence" Two groups did not differ on perceived stress	n/a	n/a	Effective (Between group mean difference = −2.55, p = 0.008)	n/a	Not effective (details not provided)	Some Concerns
Zernicke, 2014	Synchronous online virtual classroom session with recordings and videos for additional home practice	Significant effects for both QOL and perceived stress	Effective (d =0.44, p = .049)	n/a	n/a	n/a	Effective (d = 0.49, p = .021)	Some Concerns

MBCT = Mindfulness-based cognitive therapy; CCRF = Chronic cancer-related fatigue; MBSR = Mindfulness-based stress reduction; TAU = Treatment as usual; QOL = Quality of life; eMBI = Internet-based mindfulness-based intervention, n/a = not available

Discussion

Summary of Main Results

This systematic review of eMBIs for cancer patients and survivors included seven studies with a total of 826 participants. To our knowledge, this review is the first of its kind, and thus has some important implications for future research and for the application in clinical practice. With regards to the objectives of this review, there are three perspectives for discussion.

First, eMBIs were positively effective for anxiety symptom, and was either not proven or revealed to be not positively effective for other outcome measures. Those outcomes align with existing systematic reviews addressing broader patient characteristics (Fish et al., 2016; Spijkerman et al., 2016), which summarized the effects of eMBIs. Both systematic reviews reported positive effects of eMBI on anxiety. However, they also reported positive effects of eMBIs on depression and perceived stress. Different study populations might explain this discrepancy. Unlike this review, those two reviews had broader populations including other chronic disease patients and healthy populations. We were not able to assess the effectiveness of eMBI compared to face-to-face MBI due to the limited number of included studies. There was only one study (Compen 2018) that compared the two interventions, which indicated eMBI as similarly effective as MBI. However, the study was not intended to directly compare eMBI and MBI due to limited sample size. Future research is needed to assess this point.

Second, all the studies were conducted in Europe, North America and Australia. Because eMBI is relatively new, cross-cultural validation is not yet warranted. To our

knowledge cross-cultural assessment of MBI with cancer patients have not been thoroughly discussed.

Third, eMBI may be the most effective when delivered as a series of 1-week module session with or without therapist involved. However, we found only two different modes of delivery. Further research should focus on alternative ways of delivering the intervention. There are reviews indicating that online psychology interventions without therapist involvement have lower effects (Spek et al., 2007), which might have already changed in the last decade or may change in the near future.

Risk of Bias

We rated the risk of bias for all studies using the RoB2 tool (Higgins, 2019) and created a 'Risk of Bias Summary' table. Due to the nature of eMBI interventions, where patients are also assessors of outcomes, none of the studies were double-blinded. This raises a strong suspicion of bias due to deviations from the intended intervention.

Another limitation we found was that the rates of dropouts were high in most of the studies with the potential reasons mentioned in the ‘result’ section. Because of this, all studies were either high risk of bias or some concerns in the overall assessment. Qualitative research examining the reasons for dropout is critical to improve the effectiveness of eMBIs. One potential way is providing apps, which could somehow ease the high intensity of the mindfulness program and with simple and smooth usability. Finally, overall assessment resulted in one low risk, four some concerns and two high risks.

Limitations

Similar to other psycho-oncology research, the majority of the patients included in the studies were middle-aged patients with breast cancer. Although this is consistent with the characteristics of patients in the real world seeking psycho-oncology support (Garsen et al, 2016), this might limit generalizability to patients with other types of cancer. Also, as mentioned in our discussion section, studies took place in Europe, North America, and Australia, which limits generalizability to patients in the other region of the world with different cultural backgrounds.

Potential Biases in the Review Process

This review followed PRISMA guide line (Moher et al., 2009) and RoB 2 (Sterne et al., 2019) and both reviewers and supervisor have at all times attempted to avoid or minimize any biases in the review process. We believe we have identified and included in this review all potentially relevant studies. Two reviewers systematically extracted trial data.

Author's Conclusions

Implications for Practice

This study suggests eMBI is effective for cancer patients and survivors suffering from anxiety symptoms. Having stated that, although it may be effective to reduce anxiety symptoms, there are notable factors to consider when implementing it in the real-world clinical setting. User engagement and the acceptability and feasibility of the intervention are critically important.

Implications for Research

There are substantial implications for future research into the use of technology to endorse eMBI. We experienced challenges synthesizing data from the included studies, due to inconsistencies in measurement scales used across the study populations. Future studies should consider using commonly accepted measurement scales.

Acknowledgement

I would like to thank/acknowledge Yasumasa Segawa, MPH candidate at Columbia University, who helped with study selection, data extraction, and risk of bias assessment; Ms. Sato from the St. Lukes International University Library helped with the database search and identification of relevant studies and Professor Satomi Sato and Professor Kevin Urayama for providing insightful feedbacks. As for providing clinical inputs, I would like to acknowledge Dr. Tomohiro Ochi who is a breast surgeon as well as a classmate of St. Lukes International University SPH; and also Dr. Ui Yamada who is a psychosomatic medicine doctor at St. Lukes International University.

Finally, I would like to acknowledge the contributions of my supervisor Katharina da Silva Lopes PhD at St. Luke's International University for her precise, prompt and earnest guidance throughout the process. Without her dedication, this study would not have been completed.

References

References marked with an asterisk indicate studies included in the meta-analysis.

*Bruggeman-Everts, F. Z., Wolvers, M. D. J., van de Schoot, R., Vollenbroek-Hutten, M. M. R., & Van der Lee, M. L. (2017). Effectiveness of two web-based interventions for chronic cancer-related fatigue compared to an active control condition: Results of the "fitter na kanker" randomized controlled trial. *Journal of Medical Internet Research*, *19*(10), e336. https://doi.org/10.2196/jmir.7180

Carlson, L. E., Angen, M., Cullum, J., Goodey, E., Koopmans, J., Lamont, L., MacRae, J. H., Martin, M., Pelletier, G., Robinson, J., Simpson, J. S. A., Speca, M., Tillotson, L., & Bultz, B. D. (2004). High levels of untreated distress and fatigue in cancer patients. *British Journal of Cancer*, *90*(12), 2297 – 2304. https://doi.org/10.1038/sj.bjc.6601887

Compen, F. R., Bisseling, E. M., Schellekens, M. P., Jansen, E. T., van der Lee, M. L., & Speckens, A. E. (2017). Mindfulness-based cognitive therapy for cancer patients delivered via internet: qualitative study of patient and therapist barriers and facilitators. *Journal of Medical Internet Research*, *19*(12), e407. https://doi.org/10.2196/jmir.7783

*Compen, F., Bisseling, E., Schellekens, M., Donders, R., Carlson, L., van der Lee, M., & Speckens, A. (2018). Face-to-face and internet-based mindfulness-based cognitive therapy compared with treatment as usual in reducing psychological

distress in patients with cancer: A multicenter randomized controlled trial. *Journal of Clinical Oncology, 36*(23), 2413 – 2421. https://doi.org/10.1200/JCO.2017.76.5669

Ferlay, J., Colombet, M., Soerjomataram, I., Mathers, C., Parkin, D. M., Piñeros, M., Znaor, A., & Bray, F. (2019). Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *International Journal of Cancer*, *144*(8), 1941 – 1953. https://doi.org/10.1002/ijc.31937

Fish, J., Brimson, J., & Lynch, S. (2016). Mindfulness interventions delivered by technology without facilitator involvement: What research exists and what are the clinical outcomes? *Mindfulness*, *7*(5), 1011 – 1023. https://doi.org/10.1007/s12671-016-0548-2

Higgins, J. P. T., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, A. D., Savovic, J., Schulz, K. F., Weeks, L., Sterne, J. A. C., Cochrane Bias Methods Group, & Cochrane Statistical Methods Group. (2011). The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*, *343*(oct18 2), d5928–d5928. https://doi.org/10.1136/bmj.d5928

Kabat-Zinn, J. (2013). *Full catastrophe living, revised edition: How to cope with stress, pain and illness using mindfulness meditation*. Hachette UK.

*Messer, D. (2018). *Effects of internet training in mindfulness meditation on variables related to cancer recovery* (2017-29365-033; Issues 9-B(E)) [ProQuest Information & Learning]. APA PsycInfo. http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=2017-29365-033&site=ehost-live

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & The PRISMA Group. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine*, *6*(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

*Nissen, E. R., O'Connor, M., Kaldo, V., Højris, I., Borre, M., Zachariae, R., & Mehlsen, M. (2020). Internet-delivered mindfulness-based cognitive therapy for anxiety and depression in cancer survivors: A randomized controlled trial. *Psycho-Oncology*, *29*(1), 68 – 75. https://doi.org/10.1002/pon.5237

*Rosen, K. D., Paniagua, S. M., Kazanis, W., Jones, S., & Potter, J. S. (2018). Quality of life among women diagnosed with breast Cancer: A randomized waitlist controlled trial of commercially available mobile app-delivered mindfulness training. *Psycho-Oncology*, *27*(8), 2023 – 2030. https://doi.org/10.1002/pon.4764

Russell, L., Ugalde, A., Milne, D., Austin, D., & Livingston, P. M. (2018). Digital characteristics and dissemination indicators to optimize delivery of internet-supported mindfulness-based interventions for people with a chronic condition:

Systematic review. *JMIR Mental Health*, *5*(3), e53. https://doi.org/10.2196/mental.9645

*Russell, L., Ugalde, A., Orellana, L., Milne, D., Krishnasamy, M., Chambers, R., Austin, D. W., & Livingston, P. M. (2019). A pilot randomised controlled trial of an online mindfulness-based program for people diagnosed with melanoma. *Supportive Care in Cancer*, *27*(7), 2735 – 2746. https://doi.org/10.1007/s00520-018-4574-6

Searight, H. R., & Montone, K. (2017). Profile of Mood States. In V. Zeigler-Hill & T. K. Shackelford (Eds.), *Encyclopedia of Personality and Individual Differences* (pp. 1 – 6). Springer International Publishing. https://doi.org/10.1007/978-3-319-28099-8_63-1

Shapiro, S. L., Carlson, L. E., Astin, J. A., & Freedman, B. (2006). Mechanisms of mindfulness. *Journal of Clinical Psychology*, *62*(3), 373 – 386. https://doi.org/10.1002/jclp.20237

Spek, V., Cuijpers, P., Nyklíček, I., Riper, H., Keyzer, J., & Pop, V. (2007). Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: A meta-analysis. *Psychological Medicine*, *37*(3), 319 – 328. https://doi.org/10.1017/S0033291706008944

Spijkerman, M. P. J., Pots, W. T. M., & Bohlmeijer, E. T. (2016). Effectiveness of online mindfulness-based interventions in improving mental health: A review and meta-analysis of randomised controlled trials. *Clinical Psychology Review*, *45*, 102 – 114. https://doi.org/10.1016/j.cpr.2016.03.009

Spinhoven, P., Ormel, J., Sloekers, P. P., Kempen, G. I., Speckens, A. E., & Van Hemert, A. M. (1997). A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychological Medicine*, *27*(2), 363 – 370. https://doi.org/10.1017/s0033291796004382

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H.-Y., Corbett, M. S., Eldridge, S. M., Emberson, J. R., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., … Higgins, J. P. T. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ (Clinical Research Ed.)*, *366*, l4898. https://doi.org/10.1136/bmj.l4898

Toivonen, K. I., Zernicke, K., & Carlson, L. E. (2017). Web-based mindfulness interventions for people with physical health conditions: Systematic review. *Journal of Medical Internet Research*, *19*(8), e303. https://doi.org/10.2196/jmir.7487

Upton, J. (2013). Beck Depression Inventory (BDI). In M. D. Gellman & J. R. Turner (Eds.), *Encyclopedia of Behavioral Medicine* (pp. 178 – 179). Springer. https://doi.org/10.1007/978-1-4419-1005-9_441

van Helmondt, S. J., van der Lee, M. L., & de Vries, J. (2017). Translation and validation of the Dutch version of the Fear of Cancer Recurrence Inventory (FCRI-NL). *Journal of Psychosomatic Research*, *102*, 21 – 28. https://doi.org/10.1016/j.jpsychores.2017.09.001

Walker, J., Hansen, C. H., Martin, P., Symeonides, S., Ramessur, R., Murray, G., & Sharpe, M. (2014). Prevalence, associations, and adequacy of treatment of major depression in patients with cancer: A cross-sectional analysis of routinely collected clinical data. *The Lancet Psychiatry*, *1*(5), 343 – 350. https://doi.org/10.1016/S2215-0366(14)70313-X

*Zernicke, K. A., Campbell, T. S., Speca, M., McCabe-Ruff, K., Flowers, S., & Carlson, L. E. (2014). A randomized wait-list controlled trial of feasibility and efficacy of an online mindfulness–based cancer recovery program: The etherapy for cancer applying mindfulness trial. *Psychosomatic Medicine*, *76*(4), 257 – 267. https://doi.org/10.1097/PSY.0000000000000053

Appendices

Appendix A.

Risk of Bias Judgments and Comments

Bruggeman-Evert, 2017

Bias	Judgement	Support for Judgement
Domain 1: Risk of bias arising from the randomization process	High	Baseline HADS of intervention group was higher than one of control group. It is reported that there was algorithm error of randomization.
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	High	Authors noted "Neither researchers, participants, nor therapists were blind to treatment."
Domain 3: Missing outcome data	High	38% (21/55) dropped out. Potential reasons are 1) the high intensity of the program, 2) poor usability of online website, and 3) difficulty in communicating in writing with the therapist."
Domain 4: Risk of bias in measurement of the outcome	Some Concerns	It is possible that participants interested in meditation have completed.
Domain 5: Risk of bias in selection of the reported result	Low	No particular problem found.
Overall	High	

Compen, 2018

Bias	Judgement	Support for Judgement
Domain 1: Risk of bias arising from the randomization process	Low	Computerized allocation sequence. It was designed by an independent researcher.
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	High	Intervention was not blinded for participants, researchers nor therapists.
Domain 3: Missing outcome data	High	30% (63/90) dropped out.
Domain 4: Risk of bias in measurement of the outcome	Some Concerns	It is possible that participants interested in meditation have completed.
Domain 5: Risk of bias in selection of the reported result	Low	No particular problem found.
Overall	Some Concerns	

Messer, 2019

Bias	Judgement	Support for Judgement
Domain 1: Risk of bias arising from the randomization process	Low	Random assignment was performed through website algorithm. The algorithm first stratified by recruitment source and then allocated to treatment or usual care conditions.

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	High	Participants were not blind to treatment.
Domain 3: Missing outcome data	Low	No particular problem found.
Domain 4: Risk of bias in measurement of the outcome	Low	No particular problem found.
Domain 5: Risk of bias in selection of the reported result	Low	No particular problem found.
Overall	Low	

Nissen, 2020

Bias	Judgement	Support for Judgement
Domain 1: Risk of bias arising from the randomization process	Low	No particular problem found.
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	High	Intervention was not blinded for participants, researchers nor therapists.
Domain 3: Missing outcome data	High	29% (74/104) dropped out.
Domain 4: Risk of bias in measurement of the outcome	Some Concerns	It is possible that participants interested in meditation have completed.
Domain 5: Risk of bias in selection of the reported result	Low	No particular problem found.
Overall	Some concerns	

Rosen, 2018

Bias	Judgement	Support for Judgement
Domain 1: Risk of bias arising from the randomization process	Some concerns	Health Literacy and Education level was higher in the intervention group.
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	High	Intervention was not blinded for participants, researchers nor therapists.
Domain 3: Missing outcome data	High	46% (31/57) dropped out. Authors noted "Overall, baseline QOL was higher among completers (M=98.80; SD=20.20) compared to non-completers (M=82.56; SD=26.76), t (59.25) =-3.29, p=0.002. "
Domain 4: Risk of bias in measurement of the outcome	Some concerns	Potentially participants interested in meditation have higher rate of completion.
Domain 5: Risk of bias in selection of the reported result	Some concerns	Unclear due to lack of information
Overall	High	

Russell, 2018

Bias	Judgement	Support for Judgement

Domain 1: Risk of bias arising from the randomization process	Low	No particular problem found.
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	High	Neither researchers, participants, nor therapists were blind to treatment.
Domain 3: Missing outcome data	High	30% (14/46) dropped out.
Domain 4: Risk of bias in measurement of the outcome	Some Concerns	Potentially participants interested in meditation have higher rate of completion.
Domain 5: Risk of bias in selection of the reported result	Low	No particular problem found.
Overall	Some Concerns	

Zernicke, 2014

Bias	Judgement	Support for Judgement
Domain 1: Risk of bias arising from the randomization process	Some concerns	Although the process seems robust, allocated cancer type was significantly different (Breast cancer was twice as large for intervention group)
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	High	Intervention was not blinded for participants, researchers nor therapists.
Domain 3: Missing outcome data	Some concerns	17% (5/30) dropped out.
Domain 4: Risk of bias in measurement of the outcome	Low	No particular problem found.
Domain 5: Risk of bias in selection of the reported result	Low	No particular problem found.
Overall	Some concerns	

Appendix B

Search Strategies for Databases

Search key for PubMed*:

#1 neoplasms[MeSH Terms]

#2 cancer

#3 oncology

#4 tumor

#5 tumour

#6 Psycho-Oncology[MeSH Terms]

#7 psychooncology

#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#9 Mindfulness[MeSH Terms]

#10 mindfulness-based intervention

#11 mindfulness-based cognitive behavioral therapy

#12 mindfulness-based stress reduction

#13 mbi

#14 mbct

#15 mbsr

#16 mindful*

#17 meditat*

#18 acceptance and commitment therapy

#19 embi

#20 embct

#21 etherap*

#22 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21

#23 randomized controlled trial

#24 randomized control trial

＃25 randomised controlled trial

＃26 randomised control trial

＃27 randomized

＃28 randomised

＃29 random allocation

＃30 randomly

＃31 controlled clinical trial

＃32 clinical trials as topic

＃33 rct

＃34 phase3

＃35 phase 3

＃36 phase III

＃37 P3

＃38 PIII

＃39 clinical trial, phase iii

＃40 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39

＃41 #8 AND #22 AND #40

*The above master search key was transformed to other databases in keeping with specific databases' search requirements.