INTEGRATIVE CARE (C LAMMERSFELD, SECTION EDITOR)

Mind-Body Therapies in Cancer: What Is the Latest Evidence?

Linda E. Carlson^{1,2} • Erin Zelinski² • Kirsti Toivonen³ • Michelle Flynn³ • Maryam Qureshi³ • Katherine-Ann Piedalue³ • Rachel Grant⁴

Published online: 18 August 2017 © Springer Science+Business Media, LLC 2017

Abstract

Purpose of Review Many people living with cancer use complementary therapies, and some of the most popular are mindbody therapies (MBTs), including relaxation and imagery, hypnosis, yoga, meditation, tai chi and qigong, and art therapies. The efficacy of these modalities was reviewed by assessing recent findings in the context of cancer care.

Recent Findings These therapies show efficacy in treating common cancer-related side effects, including nausea and vomiting, pain, fatigue, anxiety, depressive symptoms and improving overall quality of life. Some also have effects on biomarkers such as immune function and stress hormones. Overall studies lack large sample sizes and active comparison groups. Common issues around clearly defining treatments including standardizing treatment components, dose, intensi-ty, duration and training of providers make generalization across studies difficult.

Summary MBTs in cancer care show great promise and evidence of efficacy for treating many common symptoms.

This article is part of the Topical Collection on Integrative Care

Linda E. Carlson lcarlso@ucalgary.ca

> Erin Zelinski erin.zelinski1@ucalgary.ca

Kirsti Toivonen kirsti.toivonen@ucalgary.ca

Michelle Flynn michelle.flynn1@ucalgary.ca

Maryam Qureshi mquresh@ucalgary.ca

Katherine-Ann Piedalue klpiedal@ucalgary.ca

Future studies should investigate more diverse cancer populations using standardized treatment protocols and directly compare various MBTs to one another.

Keywords Complementary therapies · Integrative oncology · Imagery · Relaxation · Hypnosis · Mediation · Yoga · Tai chi · Qigong · Creative therapies · Art therapy · Anxiety, depression, quality of life, fatigue, pain

Introduction

Large numbers of cancer patients report use of and interest in complementary therapies during cancer treatment, including MBTs [1]. Reasons for use are most often to improve quality of life, to treat or be good to themselves, to strengthen the immune system and to inspire hope. Smaller numbers of patients use these therapies to treat specific symptoms like pain

Rachel Grant rachel.grant2@ucalgary.ca

- ¹ Tom Baker Cancer Centre, Holy Cross Site, 2202 2nd St SW, Calgary, AB T2S 3C1, Canada
- ² Department of Oncology, University of Calgary, Holy Cross Site, 2202 2nd St SW, Calgary, AB T2S 3C1, Canada
- ³ Department of Psychology, University of Calgary, 2500 University Drive NW, Calgary, AB T2N 1N4, Canada
- ⁴ Cumming School of Medicine, University of Calgary, 3280 Hospital Drive NW, Calgary, AB T2N 4Z6, Canada



and fatigue. The most popular and commonly researched MBTs are imagery and relaxation, hypnosis, yoga, meditation, tai chi and qigong, and art therapies. In this paper we devote a section to each of these, therein describing the therapy then critically summarizing the current evidence base for its efficacy in cancer care, which are summarized in Table 1. Sections follow on common methodological issues across these MBTs, and suggestions for future directions for MBT research in oncology.

Imagery and Relaxation

Description

Guided imagery refers to "guiding" an individual's imagination to evoke one or more of the senses in order to access physical, emotional and spiritual dimensions to affect bodily change [2]. Guided imagery techniques generally involve guiding the imagination toward places (environmental or situational) that help an individual feel calm, safe, happy, content and relaxed [3]. Goals may be specific (e.g. slowing heart rate, reducing pain) or general (e.g. promote mental well-being). Imagery is often combined with progressive or passive muscle relaxation to elicit the "relaxation response", a set of physiological reactions including decreased heart rate, respiration rate and blood pressure [4].

Research Results

While early studies of imagery/relaxation from the 1980s and 1990s reported some evidence for reducing pain intensity as well as affect, mood, control over pain and functional status [5], these studies often had methodological weaknesses such as small sample sizes, highly variable interventions, lack of information regarding treatment fidelity and insufficient reporting of statistics for calculating effect sizes. A 2005 review of six randomized controlled trials (RCTs) suggested improvements in depressive symptoms, anxious symptoms and quality of life [3].

In 2014, the Society for Integrative Oncology published recommendations for integrative therapies in breast cancer

Table 1	Summary	of MBT	efficacy
---------	---------	--------	----------

survivors and deemed there is strong evidence for reduced depressive symptoms and mood disturbance following relaxation [6]. In addition, they concluded there was at least moderate evidence for small improvements in anxious symptoms and stress, quality of life and physical functioning, and chemotherapy-induced nausea and vomiting following relaxation, guided imagery and progressive muscle relaxation, respectively [6]. Guided imagery has also been recommended by the National Comprehensive Cancer Network (NCCN) to aid in reducing nausea and vomiting [7].

Recent RCTs investigated multiple symptoms and included appropriate power calculations to determine sample size, and randomization completed by an independent third party [8•, 9•]. One study compared pleasant guided imagery plus progressive muscle relaxation (four weekly supervised sessions and daily unsupervised sessions lasting approximately 30 min each) to control in 208 individuals receiving chemotherapy for breast and prostate cancer [9•]. The intervention resulted in reduced symptoms of pain, fatigue, anxiety, depression, nausea, vomiting and retching; and improvements in some facets of health-related quality of life. A further strength of this study is that patient's carers, members of the research team and outcome assessors were blinded; a potential source of bias was the lack of an intent-to-treat analysis.

Another recent study compared relaxation plus guided imagery (1 h training plus 20 min of daily home practise for a week with a CD) and chemotherapy self-care education to chemotherapy self-care education alone in 65 individuals undergoing first-time chemotherapy for breast cancer [8•]. The intervention resulted in greater improvements in distress, insomnia, bloating, numbness, anxious symptoms and depressive symptoms; but no group differences were observed in several other outcomes (e.g. nausea, pain, fatigue).

Hypnosis

Description

The American Psychological Association (Division 30) defines hypnosis as "a state of consciousness involving focused

MBT	Strongest effects	Other possible effects
Relaxation/imagery	Mood, depression, CINV	Stress, QL, pain, fatigue, insomnia
Hypnosis	Anxiety, pain, CINV	Distress
Meditation	Stress, anxiety, depression, QL	Fatigue, insomnia
Yoga	Stress, anxiety, depression, QL	Fatigue, insomnia, physical function
Tai chi/qigong	Fatigue, balance	Depression, anxiety
Art therapy	QL, mood, depression	Anxiety

attention and reduced peripheral awareness characterized by an enhanced capacity for response to suggestion" [10]. The practice is generally comprised of a series of guided phases of physical relaxation and attention control beginning with an introduction stage and followed by a process of progressive relaxation (induction) using imagery, deepening techniques (further relaxation) and an offering of symptom specific suggestion. The use of hypnosis in cancer treatment dates back to the 1800s (referred to as "magnetic sleep") at which time it was used in lieu of anaesthesia during breast cancer surgery [11].

Research Results

Hypnosis has been shown to effectively diminish anxiety without the undesirable side effects associated with anxiolytic medication [12, 13]. Recently, Chen et al. [14•] performed a meta-analysis exploring the effect of hypnosis on anxiety in cancer patients and sought to both calculate the overall effect size and identify moderators. The study reported a moderate effect size in both paediatric and adult populations, and provided evidence to support therapist-guided hypnosis as generally superior to the self-directed variation in reducing anxiety [14•, 15]. Identifying and quantifying the discrepancy between the two major types of hypnosis (guided vs. self-directed) is a clear strength of this study as it is a recurrent question in some of the earlier hypnosis literature. As a caveat to this result, numerous studies, such as a recent analysis by Braggard et al. [16•], have exclusively explored the use of self-hypnosis to moderate pain and psychological distress in breast cancer patients, demonstrating a clear effect of selfhypnosis in mitigating emotional distress, insomnia and in demonstrating global improvement in quality of life [16•, 17].

To explore the use of hypnosis in the management of pain, Elkins et al. [17] conducted a review of the literature on chronic pain, including a section on cancer patients. Their work suggests that hypnotic interventions for chronic pain in this population have clear benefits that in many cases persisted over a number of months. Moreover, in many cases hypnosis demonstrated superior outcomes to comparative therapies (i.e. physical therapy). Such benefits also appear to extend to postsurgical pain as demonstrated by Montgomery et al. [18] who conducted a RCT to investigate the use of hypnosis prior to cancer surgery and its effect on sedative use and post-surgical pain. Not only did the intervention demonstrate a significant decrease in the need for intraoperative analgesia, but also decreased post-surgical pain outcomes, emotional distress and nausea. This study was remarkable for its inclusion of a costeffectiveness analysis that provided strong evidence that hypnosis reduces the clinical cost to institutions. On a similar note to pain and post-intervention distress, Richardson et al. [19] performed a meta-analysis highlighting the role of hypnosis in mitigating chemotherapy-induced nausea and vomiting (CINV), and demonstrated a large effect size in comparison with CBT. Considering the morbidity and emotional burden of post-surgical pain and CINV, such results strongly encourage the use of hypnosis as an adjunct to cancer care.

Meditation

Description

Meditation is a mind-body therapy derived most strongly from Buddhist practices [20], but there are many different forms (Table 1). At its most basic, meditation is a group of selfregulation practices focused on training attention and awareness to bring mental processes under greater voluntary control [21]. Most meditation practices have four elements in common: a quiet location with few distractions; a specific, comfortable posture achieved by sitting or lying down; a focus of attention; and an open attitude of letting thoughts come and go naturally without judgement [21]. The focus of attention may be on a specific target, such as the breath or a repeated sound or mantra (known as concentration meditation). The two most commonly applied types of meditation in health care are Transcendental Meditation (TM) and Mindfulness-Based Stress Reduction (MBSR). Since the bulk of the work in cancer care has used MBSR or an adaption, thereof that will be the focus.

MBSR is a program developed by Jon Kabat-Zinn at the University of Massachusetts Medical Centre in an attempt to operationalize the purported benefits of meditation for use with various patient populations [20]. In this, the original MBSR is meant as a model that can be adapted to the unique challenges that impact different groups (e.g. heart disease, cancer, chronic pain). MBSR teaches participants to approach their daily lives from a place of non-judgemental acceptance. It has three main components, or axioms: intention, attention and attitude [22]. Intention refers to the dynamic, everchanging *whys* that brought a practitioner to a meditation practice. Attention refers to the practice of focusing on the present moment and staying in the "here-and-now" rather than future-or goal-directed behaviours. Attitude refers to taking an approach of openness or non-judgement of whatever may come.

MBSR is typically delivered in an 8-week, structured group program consisting of a range of meditation practices, including a sensate focus body scan, sitting meditation, walking meditation, loving-kindness practice and gentle Hatha yoga postures. All formal practices are designed to cultivate increasing levels of mindfulness in day-to-day life. Participants engage in home practice daily throughout the program, and each session involves teaching relevant concepts, discussions of progress and barriers to practice, and introduction and practice of new meditation modalities. Traditional MBSR programs have been adapted for specific use with cancer patient populations (e.g. Mindfulness-Based Cancer Recovery (MBCR), [23]) and these are collectively known as Mindfulness-Based Interventions (MBIs).

Research Results

There is now a large body of work investigating the efficacy of MBIs for patients with various types of cancer. This literature has been reviewed repeatedly in the last decade [24–31]. Two recent meta-analyses focused specifically on breast cancer patients, reporting large effect sizes on stress (d = 0.71) and anxiety (d = 0.73) across nine studies with various designs [31] as well as small effects on depression (d = 0.37) and medium effects on anxiety (d = 0.51) in three RCTs [29]. Another study examined 22 randomized and non-randomized studies in all types of cancers and reported moderate effect sizes on anxiety and depression in non-randomized studies and slightly smaller effects for RCTs (d = 0.60 and 0.42, respectively) [24].

Unfortunately to date most studies continue to compare MBIs to either usual care or waitlist. In one of the few recent studies to compare an MBI to another active intervention, the MINDSET trial directly compared MBCR to another active group intervention for cancer support, Supportive Expressive Therapy (SET) and a minimal intervention control condition (a 1-day stress management seminar), in over 270 distressed breast cancer patients [32, 33•]. Overall, women in MBCR improved more on stress symptoms, mood, QOL, social support, spirituality and benefit finding compared with the SET group, and these benefits were maintained over an entire year of follow-up [33•]. While much of this work has been done in breast cancer survivors, a small study of prostate cancer patients reported that participating in an 8-week mindfulness-meditation program lead to a decrease in cancer-related anxiety and improvements in global quality of life. These changes persisted over 12 months of follow-up [34].

In another adaptation, we developed an online version of the MBCR program which extends accessibility to anyone with a computer or smartphone and internet access [35, 36, 37•]. This study included a broad range of both men and women who could either be on active treatment or completed treatment within the past 3 years, with any type of cancer. The participants attended each week for 8 weeks at a set time like an in-person group, and could see and interact with the instructor and the other participants in the online classroom. The program proved feasible and showed benefits and medium effect sizes in the online MBCR group relative to controls for scores of total mood disturbance, stress symptoms and spirituality [36, 37•], of similar magnitude to in-person groups. The Society for Integrative Oncology recently reported meditation as having the highest grade of evidence for efficacy in treating symptoms of depression, anxiety and improving quality of life in breast cancer survivors [38].

Yoga

Description

Yoga is an ancient practice that has become very popular in Western countries in recent years [39]. The word yoga means "yoke", "union" or "to join". It is a philosophy that incorporates the whole body and includes working with movements and poses (asanas), meditation and breathing exercises (pranayama) [40]. These elements are intended to create harmony between mind and body, without mental distractions, and to allow for a deeper connection with one's self. Yoga postures can stimulate the nervous system, make one's muscles and joints more flexible, and relax the mind and body. The various forms of yoga emphasize different elements: some place focus on physical poses and alignment, others on breathing control and awareness, and others emphasize meditation and philosophy. The most common form of yoga practiced in North America is Hatha yoga; this is a general term for all forms of yoga that incorporate classical yoga postures and breathing exercises.

Research Results

Alongside yoga's popularity in Western culture is a growing interest in investigating its therapeutic effects in the context of cancer care. To date, well over a hundred RCTs and uncontrolled trials have been published on this topic, and multiple reviews are published each year. Studies typically assess multi-week Hatha or therapeutic/restorative yoga interventions compared to usual care on a range of self-reported outcomes. Recent reviews have examined both RCTs and uncontrolled trials of yoga therapy compared to waitlist, treatmentas-usual and active controls, during and after cancer treatment (e.g. [41, 42, 43•]. The quality of studies included in reviews is variable, and both RCTs and uncontrolled trials support yoga's efficacy in improving psychosocial outcomes such as depression, anxiety and distress [41, 42, 43•]. Few studies include follow-up periods, so it is difficult to comment on the durability of these effects. However, one review found that improvements in depressive symptoms were maintained at 3-month follow-up, while improvements in anxiety were not [42].

Reviews have also concluded that patients experience improvements in perceived stress and emotional well-being [41, 42], quality of life and spiritual well-being [41, 43•], and social function [41] immediately following completion of yoga therapy. Physical and biomedical outcomes are less frequently reported, but there is a growing body of evidence that yoga improves fatigue [42, 43•]. There is contradictory evidence regarding yoga therapy's impact on sleep among cancer patients: one 2012 review concluded that effects on sleep were small and not significant [41], though a more recent 2017 review documented significant improvements in sleep across studies [43•]. Additional studies are needed to corroborate preliminary findings regarding other physical and biomedical outcomes, such as side effects of treatment (e.g. nausea, surgical outcomes, cognitive function) and biomarkers of immunity and stress.

Chandwani et al. 2014 study [44•] provides an example of a well-designed RCT in this field. Patients with stages 0 to III breast cancer who were undergoing radiotherapy were randomized to yoga, stretching or a waitlist group. Patients in the yoga and stretching groups participated three times a week for 6 weeks. Both psychosocial and physical measures were collected, including the following: quality of life, fatigue, depression, sleep quality and saliva samples (five were collected per day for three consecutive days at baseline, end of treatment and 1, 3 and 6 months). The yoga group reported significantly greater increases in physical quality of life compared with the waitlist group at 1 and 3 months following radiotherapy. At 1, 3 and 6 months, the yoga group reported greater increases in physical functioning compared to both the stretching and waitlist groups; there were only significant differences between stretching and waitlist groups at 3 months. Similar differences between groups were found for general health. Both the yoga and stretching groups reported significant reductions in fatigue by the end of radiotherapy. No group differences emerged for mental health and sleep quality. Cortisol slope was the steepest for the yoga group, as compared to the stretching and waitlist groups, at the end of radiotherapy and 1 month afterward. In summary, this study demonstrated that yoga may improve quality of life and affect physiology associated with radiotherapy, beyond the benefits of stretching exercises alone. Importantly, these benefits appear to be sustainable over time.

Tai chi/Qigong

Description

Tai chi is a series of slow, controlled sequences of movement that are sometimes combined with qigong—the use of purposeful breath and mental focus to attain a state of mental calm and relaxation [45]. These related practices are informed by the principles of traditional Chinese medicine and martial arts [46]. Tai chi is argued to improve the lives of cancer patients through increased mind-body awareness, especially when aspects of qigong—a related practice that many argue adds a stronger meditative aspect, are incorporated. The use of tai chi/qigong in cancer care is relatively new in Western medical settings, but the benefits for elderly patients and patients with balance and mobility issues have been clearly illustrated [47]. In China, the use of tai chi/qigong has a much longer history—especially in cancer care.

Research Results

Several studies have examined the influence of tai chi/qigong on cancer health on dimensions such as overall quality of life, fatigue, sleep, pain, nausea and survival [48•]. Although effects are reported across various dimensions, certain symptoms as well as populations appear to reap larger rewards than others [48•]. Stronger effects tend to be observed along physical dimensions such as grip strength and flexibility whereas studies assessing emotional dimensions (e.g. depression, anxiety, QOL) tend to find smaller changes [48•, 49].

A number of small studies, some of which use randomization, have compared tai chi, qigong or a combination of the two to treatment as usual or other interventions; the results of these studies tend to be mixed [48•, 49]. Although some effects are observed, the sample sizes and biases introduced in these pilot-sized projects make the results difficult to interpret (for examples, see Zeng et al. [48•]. A few large-scale randomized controlled trials have been performed and these studies tend to support the utility of tai chi/qigong as a complementary cancer therapy.

For example, Campo and colleagues [50] examined the influence of a 12-week qigong program relative to a stretching intervention on fatigue and distress in 57 elderly prostate cancer survivors. The primary outcome measures were feasibility and fatigue. Feasibility was determined using class attendance and retention. Better attendance, but not better retention, was observed for the qigong group relative to the stretching group. Likewise, a significant reduction in fatigue was observed for the qigong group but not the stretching control. Distress, the secondary outcome measure of the study, was also reduced in the qigong group relative to stretching. The authors conclude that their program is a feasible, effective intervention for the management of fatigue and distress among elderly prostate cancer survivors.

Oh and colleagues compared medical qigong to treatment as usual among a heterogeneous group of cancer patients on a variety of measures including quality of life, fatigue, mood and inflammatory biomarkers [51•]. Participants in the medical qigong group took part in the 10-week group program that met for 90 min each week and were encouraged to perform 30 min of home practice daily. The medical qigong group exhibited improved overall quality of life relative to treatment as usual. Fatigue was also significantly reduced in the medical qigong group. There were similarly large reductions for depression, anxiety and fatigue as well as total mood disturbance [51•]. In addition, C-reactive protein (CRP)—an inflammatory biomarker, decreased more dramatically in the qigong group. The authors conclude that medical qigong can improve overall quality of life and mood and can reduce fatigue and inflammation.

Cognitive fog (i.e. brain fog or chemo brain) is a common complaint among cancer survivors [52]. Using a stratified randomized controlled trial design, Oh and colleagues [53] examined the influence of a medical qigong intervention relative to usual care in a population of 81 heterogeneous cancer patients who had recently completed or were currently undergoing chemotherapy on various measures of cognitive function. Patient self-report of improved cognitive function favoured the medical qigong intervention [53]. CRP also decreased more dramatically in the qigong group, further supporting the utility of medical qigong for perceived and measurable cognitive impairments during and after chemotherapy.

Creative Therapies

Description

Creative therapies may take many forms, including music therapy, expressive writing (prose or poetry), dance, drama or role playing, art appreciation, art creation (drawing, painting, sculpting) and multimodal art therapy [54–57]. In the realm of psycho-oncology, many of these branches remain relatively uncharted; however, increased research in art therapy (specifically painting and drawing) warrants an exploration of its psychological merits for cancer patients and survivors [57].

Art therapy is an alternate approach to communicating and reflecting on emotional or existential issues and is thought to activate new ways of coping, empowerment and stability [57]. Some studies have used an unstructured approach, providing participants with different visual arts materials and free reign to create what comes to mind with little to no instruction [58-60]. After this creation phase, patients are encouraged to discuss the meanings embedded in their art while the therapist provides emotional support and interpretation [55]. Semi-structured approaches often include several different stages. For example, Goetze, Geue, Buttstaedt and Singer [61] taught outpatients techniques for drawing, before teaching them to self-reflect by drawing their moods, lastly patients created a book chronicling their experiences with cancer. Luzzatto Sereno and Capps [62] used the "body outline" technique wherein participants were given a variety of colouring materials and asked to fill in the outline of a body with any colours or forms. Afterwards, patients reflected on their work and discussed how it connected to their physical and emotional well-being [55].

Research Results

The cumulative data on art therapies is split between qualitative and quantitative research. Quantitative RCTs and pre-post studies for the most part showed significant improvement in overall quality of life, mood states, depression and physical symptoms; however, effect sizes were small to medium [59, 60, 63]. One study found decreased inflammation through salivary assays [64]. However, other randomized controlled studies found no improvement in emotional expression or spirituality compared to controls [54], no change in anxiety [58] and a meta-analysis found no difference in quality of life [57].

Qualitative studies on the other hand consistently found increases in coping and communication ability, general health and quality of life [61, 64]. The variability in findings may be attributed to differences in the content, duration and frequency of interventions (i.e. one 1 h session or bi-weekly sessions for a month), as well as diverse theoretical orientations, methods (qualitative vs. quantitative) and rigour (having a control group, matching controls, random assignment). In addition, some studies used group settings while others had one-on-one sessions with a therapist. Some approaches also combined music or mindfulness with art [63, 65]. With these multimodal approaches, it is difficult to tease apart whether effects are due to art therapy or another component, further complicating conclusions. The equivocal nature of these results establishes a need for longitudinal data as the longest follow-up study was only 6 months post-intervention.

More recent studies have expanded on some of these shortcomings. Oster et al. 2014 reported on a five-year follow-up of a randomized controlled trial of art therapy, the first longitudinal study of its kind [66•]. In the original trial, breast cancer patients in active treatment were randomized to art therapy (n = 20) or a control condition (n = 22). Art therapy included one structured session per week, over 5 weeks. Women in the art therapy condition had significantly lower depression, anxiety and physical symptoms for up to 6 months, as well as significant improvements in coping strategy use [67, 68]. At the 5-year follow-up however, there were no significant differences between groups on quality of life, physical or psychological health, or coping resources. The authors suggest art therapy is most effective during active treatment, and the effects are of limited duration.

Another study examined the effects of art therapy with patients in ambulant aftercare [56•]. Patients from a variety of tumour groups chose to be controls or part of the 22-week art therapy intervention. Although there was no randomization, controls were matched to participants in the intervention group. Participants answered questionnaires

at baseline, end of intervention and 6 months after. After controlling for gender, critical life events and other forms of social support as confounders, Geue et al. [56•] found no difference in anxiety, depression or coping in groups over time. Older studies that found changes in depression and anxiety over time often used only univariate tests, and thus could not control for demographic and disease characteristics or isolate the effects of art therapy alone [54, 56•, 59, 60].

Preliminary research with ethnic minorities suggests that art as a modality for healing and expression may be especially conducive for populations where language barriers exist. Depending on the culture, creative arts may already be a central form of expression and sharing experience—in this case it would be a natural extension to use art as a form of therapy [69]. Otherwise, the kinds of art projects pursued in therapy are highly flexible, and can be tailored to reflect modalities and beliefs significant to different cultures. The latter was used in a qualitative study with Chinese breast cancer patients who completed six 2-h art sessions with a therapist

 Table 2
 Common methodological issues in MBT research

[70]. Findings suggested that this culturally and linguistically tailored program allowed Chinese patients to find meaning, and address psychosocial challenges. In light of the possible benefits for different populations, it is important to continue evaluating art therapies with rigorous methods.

Methodological Issues

There are a host of common methodological issues that arise across the various MBTs. These issues and strategies to strengthen methods are detailed in Table 2. In summary they include the following: (1) small sample sizes; (2) lack of randomization; (3) lack of comparison groups; (4) lack of therapy standardization and treatment fidelity checks; (5) variability in therapist training and credentials; (6) homogeneity in participant groups; (7) lack of long-term follow-up; (8) relying solely on self-report measures; (9) heterogeneity in treatment; (10) use of inappropriate or outdated statistical analyses; and (11) lack of blinding of participants and assessors.

Issue	Description	Potential remediation
(1) Small sample sizes	Often convenience samples are used and studies are not adequately powered to detect small or medium sized effects.	To avoid type II errors, conduct power analyses prior to recruitment to determine the necessary sample size.
(2) Lack of comparison groups	Often studies use only one group pre-post intervention designs without any comparison group.	Use a comparison group to control for the natural history of changes over time, historical factors and regression toward the mean.
(3) Lack of randomization	Comparison groups are often convenience samples of patients not interested in the therapy or other patients in the same clinics.	Randomize interested participants into intervention and control groups to establish equivalence at baseline across known and unknown factors.
 (4) Lack of therapy standardization and treatment fidelity checks 	Therapies within the same category often vary considerably in terms of content, number of sessions, delivery mode and home practice. Therapist behaviours are not routinely monitored.	Create standardized and if possible manualized interventions. Check to see that therapists are actually following the manual.
(5) Variability in therapist training and credentials	Not all therapists across any given modality have the same level of training or experience.	Choose similarly and highly trained professionals to deliver interventions. Describe the training in publications.
(6) Homogeneity in participant groups	Often studies are conducted with only one type of cancer (usually breast), and often only early stage disease.	To broaden generalizability, test interventions in other types of cancer groups, and with late stage participants.
(7) Lack of long-term follow-up	Many studies only look at pre-post intervention changes so we know little about the durability of effects.	Follow participants for several months or even years after the intervention. Check to see if they are still doing the practice in the interim.
(8) Relying solely only self-report measures	Many studies use only self-report questionnaires as outcomes.	If you use questionnaires, be sure they are appropriate, reliable and validated. Try other methods like behavioural observations, proxy reports or biomarkers.
(9) Heterogeneity in treatment phases	Often people during a variety of cancer treatment stages are studied together.	Study the effects of MBTs separately on people during and after treatment, or during palliative care.
(10) Use of inappropriate or outdated statistical analyses	Often simple <i>t</i> tests or ANOVAs are used without controlling for potential confounding variable.	Used linear mixed models or multiple regression and take into account potentially important baseline moderating factors.
(11) Lack of blinding of participants and assessors	Often testers, patients and intervention providers know which therapy participants are receiving.	It is not always possible or desirable to blind patients or providers to treatment, but assessors can be blinded to study conditions to reduce testing bias.

One of the most consistent issues that arise in MTB research is the lack of therapy standardization. In imagery for example, there is considerable variability among guided imagery scripts and there is debate as to whether standardized or tailored scripts should be used. Standardized scripts are more cost-effective and facilitate easier comparisons across studies, while unstandardized scripts may potentially be more effective when tailored to patient preferences and needs [71]. A second issue is regarding the use of pre-recorded tapes or inperson instruction. Pre-recorded materials are more cost-effective, may reduce demand characteristics and allow for home practice, while in-person instruction can allow for feedback, assurance and validation as well as result in greater treatment fidelity [3, 71].

Similarly, in yoga trials, generalizability is limited by the variety of intervention protocols used. While the majority of studies combine elements of yoga (e.g. movement, meditation and breathing), the means of intervention delivery (e.g. group vs. individual, home practice vs. instructor-led) and dose (i.e. duration and frequency of classes) varies greatly among studies. Thus, the amount of yoga practice required to produce the documented beneficial effects remains unknown. Overall, the duration, intensity, frequency and theoretical assumptions of various interventions introduce an additional level of inconsistency to the literature regarding the utility of these programs.

Future Directions

Beyond remedying the list of methodological flaws outlined above, in general future studies should examine specific interventions, in populations with specific cancer types and severities (not just breast cancer or early stage disease) undergoing specific treatments, in order to discern which interventions work, for whom and under what circumstances. Dismantling studies could help distill the most important components of an intervention. These MBTs have rarely been compared headto-head to one another in the same study; they are usually compared to usual care or more psychoeducational or physical interventions. Assessing the differential utility of various MBTs for specific symptoms would allow more specificity in recommendations. All we know now is that most of these are better than usual care across a range of symptoms, but we are not able to recommend a specific MBT that is most effective for anxiety, for example.

In terms of generalizability and reproducibility, future studies should clearly report the content of their interventions, and the training of the intervention providers. For example, guidelines are available for developing yoga interventions for use in RCTs [72], which encourage researchers to consider their rationales for selecting the yoga style, components, dose, sequence, modifications, instructors, home practice and measurements of intervention fidelity for their studies. Additionally, further improvements in the field could be propelled by the development of criteria for reporting MBIs, for example similar to the STRICTA framework for acupuncture research [73]. Further examinations of biological changes (e.g. CRP, inflammatory biomarkers, cortisol levels, gene expression, etc.) could continue to be explored so we can gain insight into the mechanisms of action which underlie the potential benefits of MBTs for cancer patients.

A final issue pertains not to the research itself but to knowledge translation and dissemination of results into clinical practice. Although the research in many areas is promising and patients indicate they would be willing to use these therapies as non-pharmacological adjuvant to cancer treatment, in most cases they have yet to be integrated into standard practice. As such, future research in this area should continue to stress integration into clinical practice and seek to provide tangible objectives and guidelines for its application.

Conclusions

This review suggests that all of these MBTs can be useful for reducing anxiety and depression symptoms and improving quality of life. However, it is unclear if there is specificity between interventions and outcomes; that is, one MBT seems equally useful to the next across most of these symptoms. An exception may be that imagery/relaxation and hypnosis have greater utility for nausea/vomiting and pain control, whereas meditation, yoga and tai chi/qigong may be more useful for improving overall quality of life, depression and anxiety. These possibilities remain to be empirically tested, however, as few studies have compared MBTs to one another for symptom control.

Acknowledgements Dr. Carlson holds the Enbridge Research Chair in Psychosocial Oncology, co-funded by the Alberta Cancer Foundation and the Canadian Cancer Society, Alberta/NWT Division. Dr. Zelinski holds a Cumming School of Medicine Postdoctoral Fellowship. Kirsti Toivonen is supported by a Canadian Institutes of Health Research Doctoral Award. Michelle Flynn is supported by a Canada Graduate Scholarship-Master's award through Canadian Institutes of Health Research. Maryam Qureshi holds the Alberta Innovates Health Research Summer Studentship for the summer of 2017.

Compliance with Ethical Standards

Conflict of Interest Linda E. Carlson has written two books about mindfulness meditation, one of the interventions reviewed in this paper, and she receives royalties for sales of these books.

Erin Zelinski declares that she has no conflict of interest. Kirsti Toivonen declares that she has no conflict of interest. Michelle Flynn declares that she has no conflict of interest. Maryam Qureshi declares that she has no conflict of interest. Katherine-Ann Piedalue declares that she has no conflict of interest. Rachel Grant declares that she has no conflict of interest. Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- King N, Balneaves LG, Levin GT, Nguyen T, Nation JG, Card C, et al. Surveys of cancer patients and cancer health care providers regarding complementary therapy use, communication, and information needs. Integr Cancer Ther. 2015;14(6):515–24.
- Achterberg J. Imagery in healing: shamanism and modern medicine. Boston; New York: New Science Library, Shambhala; Distributed in the U.S. by Random House; 1985.
- Roffe L, Schmidt K, Ernst E. A systematic review of guided imagery as an adjuvant cancer therapy. Psychooncology. 2005;14(8): 607–17.
- Benson H. The relaxation response: therapeutic effect. Science. 1997;278(5344):1694–5.
- Wallace KG. Analysis of recent literature concerning relaxation and imagery interventions for cancer pain. [review]. Cancer Nurs. 1997;20:79–87.
- Greenlee H, Balneaves LG, Carlson LE, Cohen M, Deng G, Hershman D, et al. Clinical practice guidelines on the use of integrative therapies as supportive care in patients treated for breast cancer. J Natl Cancer Inst. 2014. In press.
- National Comprehensive Cancer Network: Nausea and vomiting 2017. https://www.nccn.org/professionals/physician_gls/pdf/ antiemesis.pdf. Accessed 26 Mar 2007.
- 8.• Chen SF, Wang HH, Yang HY, Chung UL. Effect of relaxation with guided imagery on the physical and psychological symptoms of breast cancer patients undergoing chemotherapy. Iran Red Crescent Med J. 2015;17(11):e31277. This study is noteworthy for methodological rigor, employing design characteristics often missing in studies of mind-body therapies (e.g. sample size based on power calculation, randomization completed by an independent third party).
- 9.• Charalambous A, Giannakopoulou M, Bozas E, Marcou Y, Kitsios P, Paikousis L. Guided imagery and progressive muscle relaxation as a cluster of symptoms management intervention in patients receiving chemotherapy: a randomized control trial. PLoS One. 2016;11(6):e0156911. This study is noteworthy for methodological rigor, employing several design characteristics often missing in studies of mind-body therapies (e.g. blinded outcome assessment, sample size based on power calculation).
- American Psychological Association: Definitions. Retrieved Feb.15, 2017 from http://www.apa.org/topics/hypnosis/media.aspx.
- Potie A, Roelants F, Pospiech A, Momeni M, Watremez C. Hypnosis in the perioperative management of breast cancer surgery: clinical benefits and potential implications. Anesthesiol Res Pract. 2016;2016:2942416.
- 12. Kravits K. Hypnosis: adjunct therapy for cancer pain management. J Adv Pract Oncol. 2013;4(2):83.
- Sohl SJ, Stossel L, Schnur JB, Tatrow K, Gherman A, Montgomery GH. Intentions to use hypnosis to control the side effects of cancer and its treatment. Am J Clin Hypn. 2010;53(2):93–100.
- 14.• Chen P, Liu Y, Chen M. The effect of hypnosis on anxiety in patients with cancer: a meta-analysis. Worldviews Evid Based Nurs. 2017;14(3):223–36. This study was noteworthy for

methodological rigor, scope and for being the first metaanalysis to explore the impact of hypnosis on anxiety in cancer patients.

- Tefikow S, Barth J, Maichrowitz S, Beelmann A, Strauss B, Rosendahl J. Efficacy of hypnosis in adults undergoing surgery or medical procedures: a meta-analysis of randomized controlled trials. Clin Psychol Rev. 2013;33(5):623–36.
- 16.• Bragard I, Etienne AM, Faymonville ME, Coucke P, Lifrange E, Schroeder H, et al. A nonrandomized comparison study of selfhypnosis, yoga, and cognitive-behavioral therapy to reduce emotional distress in breast cancer patients. Int J Clin Exp Hypn. 2017;65(2):189–209. This study is noteworthy for its incorporation of multiple of mind-body interventions and integration with psychosocial therapies.
- Elkins G, Jensen MP, Patterson DR. Hypnotherapy for the management of chronic pain. Int J Clin Exp Hypn. 2007;55(3):275–87.
- Montgomery GH, Bovbjerg DH, Schnur JB, David D, Goldfarb A, Weltz CR, et al. A randomized clinical trial of a brief hypnosis intervention to control side effects in breast surgery patients. J Natl Cancer Inst. 2007;99(17):1304–12.
- Richardson J, Smith JE, McCall G, Richardson A, Pilkington K, Kirsch I. Hypnosis for nausea and vomiting in cancer chemotherapy: a systematic review of the research evidence. Eur J Cancer Care (Engl). 2007;16(5):402–12.
- Kabat-Zinn J. Full catastrophe living: using the wisdom of your body and mind to face stress, pain and illness. New York: Delacourt; 1990.
- Ospina MB, Bond K, Karkhaneh M, Buscemi N, Dryden DM, Barnes V, et al. Clinical trials of meditation practices in health care: characteristics and quality. J Altern Complement Med. 2008;14(10):1199–213.
- Shapiro SL, Carlson LE, Astin JA, Freedman B. Mechanisms of mindfulness. J Clin Psychol. 2006;62:373–86.
- Carlson LE, Speca M. Mindfulness-based cancer recovery: a stepby-step MBSR approach to help you cope with treatment and reclaim your life. Oakville: New Harbinger; 2010.
- Piet J, Wurtzen H, Zachariae R. The effect of mindfulness-based therapy on symptoms of anxiety and depression in adult cancer patients and survivors: a systematic review and meta-analysis. J Consult Clin Psychol. 2012;80(6):1007–20.
- Musial F, Bussing A, Heusser P, Choi KE, Ostermann T. Mindfulness-based stress reduction for integrative cancer care: a summary of evidence. Forsch Komplementmed. 2011;18(4):192– 202.
- Shennan C, Payne S, Fenlon D. What is the evidence for the use of mindfulness-based interventions in cancer care? A review. Psychooncology. 2011;20(7):681–97.
- Matchim Y, Armer JM, Stewart BR. Effects of Mindfulness-Based Stress Reduction (MBSR) on health among breast cancer survivors. West J Nurs Res. 2011;33(8):996–1016.
- Zhang MF, Wen YS, Liu WY, Peng LF, Wu XD, Liu QW. Effectiveness of mindfulness-based therapy for reducing anxiety and depression in patients with cancer: a meta-analysis. Medicine (Baltimore). 2015;94(45):897.
- 29. Cramer H, Lauche R, Paul A, Dobos G. Mindfulness-based stress reduction for breast cancer—a systematic review and meta-analysis. Curr Oncol. 2012;19(5):e352.
- Rush SE, Sharma M. Mindfulness-based stress reduction as a stress management intervention for cancer care: a systematic review. J Evid Based Complement Altern Med. 2016;22(2):348–60. doi:10. 1177/2156587216661467.
- Zainal NZ, Booth S, Huppert FA. The efficacy of mindfulnessbased stress reduction on mental health of breast cancer patients: a meta-analysis. Psychooncology. 2013l;22(7):1457–65.
- 32. Carlson LE, Doll R, Stephen J, Faris P, Tamagawa R, Drysdale E, et al. Randomized controlled trial of mindfulness-based cancer

recovery versus supportive expressive group therapy for distressed survivors of breast cancer. J Clin Oncol. 2013;31(25):3119–26.

- 33.• Carlson LE, Tamagawa R, Stephen J, Drysdale E, Zhong L, Speca M. Randomized-controlled trial of mindfulness-based cancer recovery versus supportive expressive group therapy among distressed breast cancer survivors (MINDSET): long-term follow-up results. Psychooncology. 2016;25(7):750–9. This study was the first to compare mindfulness to an active control group and demonstrate prolonged benefits of Mindfulness Based Cancer Recovery (MBCR).
- 34. Victorson D, Hankin V, Burns J, Weiland R, Maletich C, Sufrin N, et al. Feasibility, acceptability and preliminary psychological benefits of mindfulness meditation training in a sample of men diagnosed with prostate cancer on active surveillance: results from a randomized controlled pilot trial. Psychooncology. 2017;26(8):1155–63.
- 35. Zernicke KA, Campbell TS, Speca M, McCabe-Ruff K, Flowers S, Dirkse DA, et al. The eCALM trial-eTherapy for cancer applying mindfulness: online mindfulness-based cancer recovery program for underserved individuals living with cancer in Alberta: protocol development for a randomized wait-list controlled clinical trial. BMC Complement Altern Med. 2013;13:34.
- Zernicke KA, Campbell TS, Speca M, McCabe-Ruff K, Flowers S, Carlson LE. 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. Psychosom Med. 2014;76(4):257–67.
- 37.• Zernicke KA, Campbell TS, Speca M, KM MC, Flowers S, Tamagawa R, et al. The eCALM trial: eTherapy for cancer applying mindfulness. Exploratory analyses of the associations between online mindfulness-based cancer recovery participation and changes in mood, stress symptoms, mindfulness, posttraumatic growth, and spirituality. Mindfulness. 2016;7:1071. This study is noteworthy because it provides an alternative resource, such as accessing MBCR training online, along with setting a methodological approach for future research in mindfulness meditation.
- Greenlee H, DuPont-Reyes MJ, Balneaves LG, Carlson LE, Cohen MR, Deng G, et al. Clinical practice guidelines on the evidencebased use of integrative therapies during and after breast cancer treatment. CA Cancer J Clin. 2017;67(3):194–232.
- Cancer Research UK. Yoga. Retrieved from http://www. cancerresearchuk.org/about-cancer/cancers-in-general/treatment/ complementary-alternative/therapies/yoga#what. Feb 2015.
- Canadian Cancer Society. Yoga. Retrieved from http://www.cancer. ca/en/cancer-information/diagnosis-and-treatment/complementarytherapies/yoga/?region=on#ixzz4aeQtcvy0. Feb 2017.
- 41. 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 metaanalysis of randomized controlled trials. BMC Cancer. 2012;12: 559.
- 42. Zuo X, Li Q, Gao F, Yang L, Meng F. Effects of yoga on negative emotions in patients with breast cancer: a meta-analysis of randomized controlled trials. Int J Nurs Sci. 2016;3(3):299–306.
- 43.• Danhauer SC, Addington EL, Sohl SJ, Chaoul A, Cohen L. Review of yoga therapy during cancer treatment. Support Care Cancer. 2017;25(4):1357–72. This citation is of significance because it is a recent review of the topic.
- 44. 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. J Clin Oncol: Off J Am Soc Clin Oncol. 2014;32(10):1058–65. This is an important study because it is an example of a well-designed RCT investigating yoga as an intervention for cancer survivors. This study is recent and includes both psychosocial and physical measures at multiple time points.

- 45. Jahnke R, Larkey L, Rogers C, Etnier J, Lin F. A comprehensive review of health benefits of qigong and tai chi. Am J Health Promot. 2010;24(6):e25.
- Yeh GY, Wang C, Wayne PM, Phillips RS. The effect of tai chi exercise on blood pressure: a systematic review. Prev Cardiol. 2008;11(2):82–9.
- 47. Li F, Harmer P, Fisher KJ, McAuley E, Chaumeton N, Eckstrom E, et al. Tai chi and fall reductions in older adults: a randomized controlled trial. The journals of gerontology. A Biol Sci Med Sci. 2005;60(2):187–94.
- 48.• Zeng Y, Luo T, Xie H, Huang M, Cheng AS. Health benefits of qigong or tai chi for cancer patients: a systematic review and meta-analyses. Complement Ther Med. 2014;22(1):173–86. Zeng et al. is of note because it provides a recent, balanced summary of the benefits of tai chi and qigong in cancer.
- Lee MS, Choi TY, Ernst E. Tai chi for breast cancer patients: a systematic review. Breast Cancer Res Treat. 2010;120(2):309–16.
- 50. Campo R, Agarwal N, LaStayo P, O'Connor K, Pappas L, Boucher K, et al. Levels of fatigue and distress in senior prostate cancer survivors enrolled in a 12-week randomized controlled trial of qigong. J Cancer Surviv. 2014;8(1):60–9.
- 51.• Oh B, Butow P, Mullan B, Clarke S, Beale P, Pavlakis N, et al. Impact of medical qigong on quality of life, fatigue, mood and inflammation in cancer patients: a randomized controlled trial. Ann Oncol. 2010;21(3):608–14. This study is of special importance given its depth and breadth of outcomes associated with medical qigong in an RCT format.
- 52. Boykoff N, Moieni M, Subramanian SK. Confronting chemobrain: an in-depth look at survivors' reports of impact on work, social networks, and health care response. J Cancer Surviv: Res Pract. 2009;3(4):223–32.
- 53. Oh B, Butow P, Mullan B, Clarke S, Beale P, Pavlakis N, et al. Effect of medical qigong on cognitive function, quality of life, and a biomarker of inflammation in cancer patients: a randomized controlled trial. Support Care Cancer. 2012;20(6):1235–42.
- Puig A, Lee SM, Goodwin L, Sherrard PAD. The efficacy of creative arts therapies to enhance emotional expression, spirituality, and psychological well-being of newly diagnosed stage I and stage II breast cancer patients: a preliminary study. Arts Psychother. 2006;33:218–28.
- 55. Geue K, Goetze H, Buttstaedt M, Kleinert E, Richter D, Singer S. An overview of art therapy interventions for cancer patients and the results of research. Complement Ther Med. 2010;18(3):160–70.
- 56.• Geue K, Richter R, Buttstädt M, Brähler E, Singer S. An art therapy intervention for cancer patients in the ambulant aftercare—results from a non-randomised controlled study. Eur J Cancer Care. 2013;22(3):345–52. This study is noteworthy for its analytical rigour and identifying confounders, setting a methodological precedent for future research in art therapy.
- 57. Boehm K, Cramer H, Staroszynski T, Ostermann T. Arts therapies for anxiety, depression, and quality of life in breast cancer patients: a systematic review and meta-analysis. Evid Based Complement Alternat Med. 2014;2014:1–9.
- Bar-Sela G, Atid L, Danos S, Gabay N, Epelbaum R. Art therapy improved depression and influenced fatigue levels in cancer patients on chemotherapy. Psychooncology. 2007;16(11):980–4.
- Grulke N, Bailer H, Stähle S, Kächele H. Evaluation eines maltherapeutischen Angebots f
 ür onkologische Patienten in einem Akutkrankenhaus. Musik-, Tanz und Kunsttherapie. 2006;17(1):21–9.
- Nainis NA. Approaches to art therapy for cancer inpatients: research and practice considerations. Art Ther. 2008;25(3):115–21.
- 61. Götze H, Geue K, Buttstädt M, Singer S. Gestaltungskurs für onkologische Patienten in der ambulanten Nachsorge. Musik-, Tanz und Kunsttherapie. 2007;18(1):33–40.

- 62. Luzzatto P, Sereno V, Capps R. A communication tool for cancer patients with pain: the art therapy technique of the body outline. Palliat Support Care. 2003;1(2):135–42.
- 63. Monti DA, Kash KM, Kunkel EJ, Moss A, Mathews M, Brainard G, et al. Psychosocial benefits of a novel mindfulness intervention versus standard support in distressed women with breast cancer. Psychooncology. 2013;22(11):2565–75.
- 64. Wood MJM, Molassiotis A, Payne S. What research evidence is there for the use of art therapy in the management of symptoms in adults with cancer? A systematic review. Psycho-Oncology. 2011;20(2):135–45.
- 65. Jang S, Kang S, Lee H, Lee S. Beneficial effect of mindfulness-based art therapy in patients with breast cancer—a randomized controlled trial. Explore (NY). 2016;12(5):333–40.
- 66.• Öster I, Tavelin B, Egberg Thyme K, Magnusson E, Isaksson U, Lindh J, et al. Art therapy during radiotherapy—a five-year follow-up study with women diagnosed with breast cancer. Arts Psychother. 2014;41(1):36–40. To date this study is the longest follow-up for an art therapy intervention with cancer patients, probing into longitudinal outcomes.
- 67. Thyme KE, Sundin EC, Wiberg B, Öster I, Åström S, Lindh J. Individual brief art therapy can be helpful for women with breast

cancer: a randomized controlled clinical study. Palliat Support Care. 2009;7(1):87–95.

- Oster I, Svensk AC, Magnusson E, Thyme KE, Sjodin M, Astrom S, et al. Art therapy improves coping resources: a randomized, controlled study among women with breast cancer. Palliat Support Care. 2006;4(1):57–64.
- Cueva M. "Bringing what's on the inside out": arts-based cancer education with Alaska Native peoples. Pimatisiwin: J Aboriginal Indigenous Community Health. 2011;9(1).
- Lee T, Mitchell G, Liaw J, Ho G, Cheng T, Ki P, et al. Art therapy for Chinese Canadian breast cancer survivors in Toronto. J Sci Res Rep. 2015;4(5):421–9.
- Van Fleet S. Relaxation and imagery for symptom management: improving patient assessment and individualizing treatment. Oncol Nurs Forum. 2000;27(3):501.
- Sherman KJ. Guidelines for developing yoga interventions for randomized trials. Evid Based Complement Alternat Med: eCAM. 2012;2012:143271.
- MacPherson H, Altman DG, Hammerschlag R, Youping L, Taixiang W, White A, et al. Revised standards for reporting interventions in clinical trials of acupuncture (STRICTA): extending the CONSORT statement. J Evid Based Med. 2010;3(3):140–55.