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Clinical practice guidelines on the evidence-based use of integrative therapies during and following breast cancer treatment

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Abstract

Patients with breast cancer commonly use complementary and integrative therapies as supportive care during cancer treatment and to manage treatment-related side effects. However, evidence supporting the use of such therapies in the oncology setting is limited. This report provides updated clinical practice guidelines from the Society for Integrative Oncology on the use of integrative therapies for specific clinical indications during and after breast cancer treatment, including anxiety/stress, depression/mood disorders, fatigue, quality of life/physical functioning, chemotherapy-induced nausea and vomiting, lymphedema, chemotherapy-induced peripheral neuropathy, pain, and sleep disturbance. Clinical practice guidelines are based on a systematic literature review from 1990 through 2015. Music therapy, meditation, stress management, and yoga are recommended for anxiety/stress reduction. Meditation, relaxation, yoga, massage, and music therapy are recommended for depression/mood disorders. Meditation and yoga are recommended to improve quality of life. Acupressure and acupuncture are recommended for reducing chemotherapy-induced nausea and vomiting. Acetyl-L-carnitine is not recommended to

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prevent chemotherapy-induced peripheral neuropathy due to a possibility of harm. No strong evidence supports the use of ingested dietary supplements to manage breast cancer treatment-related side effects. In summary, there is a growing body of evidence supporting the use of integrative therapies, especially mind-body therapies, as effective supportive care strategies during breast cancer treatment. Many integrative practices, however, remain understudied, with insufficient evidence to be definitively recommended or avoided.

Keywords

Breast cancer; integrative therapies; complementary therapies; implementation strategies; integrative oncology; integrative medicine; music therapy; meditation; yoga; stress management; relaxation; massage; acupressure; acupuncture

INTRODUCTION

Patients with breast cancer and breast cancer survivors are frequent users of complementary and integrative therapies and there are a growing number of formal integrative oncology programs within cancer centers.[1–6] A variety of terms are used to describe such use and it is helpful at the outset to define terms. *Complementary and alternative therapies* are generally defined as any medical system, practice, or product that is not part of conventional medical care.[7, 8] Other relevant terminology includes *"complementary medicine",* which comprises therapies used as a complement alongside conventional medicine; "*alternative medicine"*, which comprises therapies used in place of conventional medicine; and "*integrative medicine*", which is the coordinated use of evidence-based complementary practices and conventional care. *Integrative oncology* refers to the use of complementary and integrative therapies in collaboration with conventional oncology care. In oncology, individuals employ complementary and integrative therapies with the intent of enhancing wellness, improving quality of life (QOL), and relieving symptoms of disease and side effects of conventional treatments. However, the evidence supporting the use of complementary and integrative therapies in the oncology setting is limited.

In November 2014, the Society for Integrative Oncology (SIO) published clinical practice guidelines to inform both clinicians and patients on the use of integrative therapies during breast cancer treatment and to treat breast cancer treatment-related symptoms.[9] SIO adapted methods established by the U.S. Preventive Services Task Force[10] to develop graded recommendations on the use of specific integrative therapies for defined clinical indications based on strength of available evidence concerning associated benefits and harms. The 2014 clinical practice guidelines were derived from a systematic review of randomized clinical trials published between 1990 and 2013 and organized by specific clinical conditions (e.g., anxiety/stress, fatigue). This review provides an updated set of clinical practice guidelines based upon a current systematic literature review of randomized controlled trials published through December 2015. In addition, this review provides detailed definitions of integrative therapies and clinical outcomes of interest, a detailed summary of the literature upon which the clinical practice guidelines are based, and suggestions for how appropriate therapies may be integrated into clinical practice.

Of note, it is important to define the use of the term “recommendation” in these clinical practice guidelines. In many settings, a clinical guideline “recommendation” infers that it be used as the standard of care and is favorable or equal compared to all other options based on best clinical evidence for benefit/risk ratio. Here, in the setting of integrative oncology, we use the term “recommendation” to infer that the therapy should be considered as a viable but not singular option for the management of a specific symptom or side effect. Few studies have conducted a head to head comparison of a given integrative therapy against a conventional treatment, and most integrative therapies are used in conjunction with standard therapy and have been studied in this manner. Moreover, combination-based approaches and the interactions of the numerous permutations of integrative and conventional treatments have not been formally investigated, such that recommendations must account for this limitation of our knowledge. Despite these limitations to the evaluation of the use of integrative therapies in the oncology setting, there is a body of well-conducted trials of specific therapies for specific conditions that provide sufficient evidence to warrant recommendations on the therapies as viable options for treating specific conditions.

This review provides clinicians and patients with updated SIO clinical practice guidelines on the use of integrative therapies to manage symptoms and side effects during and after breast cancer treatment. The clinical practice guidelines do not address breast cancer recurrence and survival endpoints as there are very few adequately powered randomized controlled trials examining the effect of integrative therapies on these outcomes. This review provides a definition of each integrative therapy that had a sufficiently large body of evidence to formulate specific recommendations. Information is also provided on how to implement the recommendations into the clinical setting, with caveats for specific clinical situations. In addition, this review summarizes pertinent meta-analyses and identifies promising areas for future investigation. The information that arose from other published reviews and meta-analyses did not change the interpretation of the findings or quality of specific trials, but the information was used to influence the establishment of specific recommendation grades based on consistency, reproducibility and assessment of potential harms and benefits. The goal of this current review is to provide clinicians and patients with practical information and tools to evaluate whether there is an evidence-base to support the use of a defined integrative therapy for a specific clinical application in the context of breast cancer.

METHODS

Systematic Review Methodology

To update the previously published clinical practice guidelines that were based upon the a systematic review of the literature from January 1, 1990 through December 31, 2013[9], we conducted a systematic review of published randomized controlled trials from January 1, 2014 through December 31, 2015 using the same search criteria and process. The process followed the methods set forth by the Institute of Medicine on clinical guideline development.[11] The following databases were searched: Embase, MEDLINE, PsychINFO, and CINAHL. As previously reported[9], trials were selected for inclusion in the systematic review if they met the following criteria: (1) peer-reviewed published randomized controlled trial; (2) available in English; (3) included ≥ 50% breast cancer patients and/or reported

results separately for breast cancer patients; (4) used an integrative therapy as an intervention during standard treatment with surgery, chemotherapy, radiation therapy, and/or hormonal therapy, or addressed symptoms and side effects resulting from diagnosis and/or treatment; and (5) addressed an endpoint of clinical relevance to breast cancer patients and survivors (Supplemental Table 1).[9] Several lifestyle and psychological interventions were excluded from current as well as previous guidelines because they have already been well summarized by other groups (e.g., diet [12, 13] and physical activity [12–14] recommendations for cancer survivors) and/or because they have a strong evidence base and are often considered to be mainstream rather than integrative or complementary (e.g., cognitive-behavioral therapy [15], psychoeducation [16], counseling [17], and support groups [16]). Other interventions excluded were in early or pilot stages of research (e.g., attention restoration therapy) or were not considered to be an integrative oncology therapy for the purposes of the SIO guidelines (e.g., prayer, spirituality). Each article was scored according to quality of design and reporting based on the Jadad scoring scale and a modified scale adapted from the Delphi scoring system.[18, 19] Finally, grades of evidence were determined for each therapy as applied to a specific clinical outcome using a modified version of the U.S. Preventive Services Task Force Grading System.[10] Grades were based upon strength of evidence, determined by the number of trials, quality of trials, magnitude of effect, statistical significance, sample size, consistency of results across studies, and whether the outcomes were primary or secondary. The highest grades (A and B) indicate that a specific therapy is recommended for a particular clinical indication. Grade A indicates there is high certainty that the net benefit is substantial, while grade B indicates there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. Grade C indicates that the evidence is equivocal, or that there is at least moderate certainty that the net benefit is small. The lowest grades (D, H, and I) indicate no demonstrated effect, suggest harm, or indicate that the current evidence is inconclusive, respectively.

Following the clinical guideline development process outlined by the Institute of Medicine, [11] drafts prepared by the SIO Guideline Working group were distributed to an interdisciplinary group of SIO internal and external reviewers. Reviewer comments, suggestions and critiques were incorporated into the final version of these guidelines.

It is important to note that as we reviewed the literature, we recognized that there is a difference between statistical and clinical significance. The graded recommendations reflect our assessment of the clinical significance based upon our assessment of the body of literature, including the importance of statistical significance with respect to the primary endpoint. We did not report on specific magnitudes of effect because of the range of outcome measures and statistical methods used across the trials, making it difficult to describe detailed data on effect sizes across all trials. Though some of the trials with small sample sizes ($n<100$) may have been methodologically sound, we downplayed their contribution to the graded recommendation because larger trials provided more information on generalizability of results to larger populations. Due to space limitations, *p*-values are reported and citations are provided to reference the primary reports for additional details.

Definitions of Complementary and Integrative Therapies [20, 21]

Below are definitions listed alphabetically for each of the complementary and integrative therapies that received a Grade A, B, C, D or H in the updated clinical practice guidelines presented here. Table 1 displays the graded recommendations[9]. Table 2 provides background information on the specific training, licensure, and professional organizations associated with each therapy. If a therapy is known to have a specific contraindication or caution, it is noted in the description. The descriptions include statements on how the therapies are often used by cancer patients and survivors, but do not indicate the level of evidence supporting such use. The guideline recommendations provide the summary of the evidence on the use for specific conditions. In addition to the information provided below, there are continuously updated well-referenced websites that can provide additional details on the range of therapies, including Natural Medicines (https://www.naturalmedicines.therapeuticresearch.com), Memorial Sloan Kettering Cancer Center's *About Herbs* website (https://www.mskcc.org/cancer-care/treatments/symptom-management/integrative-medicine/herbs), and the National Cancer Institute's Office of Cancer Complementary and Alternative Medicine CAM Therapies: A-Z website (https://cam.cancer.gov/health_information/cam_therapies_a-z.htm).

Acetyl-L-carnitine—Acetyl-L-carnitine is a dietary supplement that some patients use to treat cancer-related fatigue by enhancing energy and lowering inflammation in the body[22]. It has shown to be effective at preventing and treating diabetic neuropathy and, therefore, was of interest to examine in the context of chemotherapy-induced peripheral neuropathy. It is a substance made in muscle and liver tissue and is found in foods including meats, poultry, fish, and some dairy products.

Acupuncture—Acupuncture involves the stimulation of specific points, (i.e., acupoints) by penetrating the skin with thin, solid, metallic needles.[23, 24] A variation of acupuncture includes electroacupuncture, in which a small electric current is passed along acupuncture needles[25] to provide a stronger stimulus than acupuncture alone, with distinct effects suggested by functional MRI [25, 26]. Acupuncture has been practiced in Asia for thousands of years as a component of traditional medicine systems (e.g., traditional forms of Chinese, Japanese and Korean medicine) and is thought to stimulate the flow of a form of energy called *qi* (chee) throughout the body. [27] Traditional Chinese acupuncture, commonly used in North America, requires needle manipulation to produce a *de qi* sensation (a soreness, fullness, heaviness, or local area distension[28, 29]), along with a period of time of rest with the placed needles.[30] This is posited to remove energetic blockages, thus reestablishing homeostasis. The mechanisms for acupuncture's effects are not well understood but are thought to function in part through modulation of specific neuronal/cortical pathways.[31] Acupuncture practice typically requires formal education through schools, training programs, and certifications (see Table 2). Acupuncture is often used in the oncology setting for chemotherapy-induced nausea/vomiting (CINV), pain management, musculoskeletal complaints, hot flashes, fatigue, stress, anxiety and sleep disorders. The practice of acupuncture in North American is regulated by some U.S. states and Canadian provinces and territories (see Table 2)

Acupressure—Acupressure draws on the same knowledge and philosophical system as acupuncture. A trained therapist, or the patient, uses his/her hands and fingers, or possibly a device to apply pressure to specific points on the body (acupoints), in contrast to metallic needles. Practices can range from stimulating a single point or a combination of points to achieve the intended outcome. In the oncology setting, acupressure is often used for CINV pain, stress management and fatigue.

Aloe Vera—*Aloe vera* gel is derived from the leaves of the perennial succulent plant, *Aloe vera* (Liliaceae). It is typically applied topically or ingested in the form of a clear thick gel.[22] *Aloe vera* gel is found in multiple skin products, such as lotions, creams, and sunblock. *Aloe vera* is used as a topical ointment to heal wounds, sunburn, insect bites, and skin conditions including psoriasis and frostbite.[32] It oncology, it is typically used with the goal of healing surgical wounds or preventing or treating radiation induced dermatitis.

Ginger—Ginger (*Zingiber officianale*) comes from the rhizome or root of a tropical plant with green-purple flowers and an aromatic stem.[22, 33] Ginger can be used as a food in cooking and for medicinal purposes. In Asian medicine, ginger is used to treat stomach aches, nausea, and diarrhea. For cancer patients, it has been studied for the treatment of chemotherapy-induced nausea and vomiting (CINV). Ginger is available in capsule form, fresh as a root, as a tea, as a candy, or in very diluted quantities in ginger ale. Ginger supplementation should not be used in perioperative settings or in patients with bleeding disorders due to potential risk for increased bleeding.[32]

Ginseng—Ginseng is derived from a plan root and has been used to treat certain medical problems.[22] There are two common types of ginseng used, Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*), while the herb called Siberian ginseng or eleuthero is not a true ginseng.[32] Asian and American ginsengs are used to boost the immune system and promote well being and stamina. Ginseng comes in capsule form made of ground ginseng, extracts, and teas as well as creams and other products for topical use. Taken as an herbal supplement, ginseng is often used to treat cancer-related fatigue.[32] Side effects of taking ginseng may include headaches, breast tenderness and menstrual irregularities, sleep problems, restlessness, rapid heart rate, low blood sugar, allergic reactions, and gastrointestinal problems.[32]

Glutamine—Glutamine is a non-essential amino acid used in the biosynthesis of proteins and is primarily synthesized in skeletal muscle.[32] Most of the glutamine synthesized in the body is utilized by the intestinal tract. Glutamine has numerous biological functions including protein and lipid synthesis, regulation of acid-base balance in the kidney, and as an important mitochondrial cellular energy source. Normally the body can synthesize its own glutamine; however, during a critical illness such as cancer not enough glutamine is made, leading to problems such as fatigue and muscle wasting. Glutamine has been used as an oral supplement in cancer patients to reverse cachexia in patients with advanced cancer. It has also been used for CINV in cancer patients. Glutamine can be obtained from food or supplements, with important food sources being beef, pork, chicken, fish, eggs, milk, dairy products, wheat, cabbage, beets, beans, spinach, and parsley.[32]

Guarana—Guarana is an herbal supplement from the guarana plant (*Paullinia cupana*) native to the Amazon basin.[32] Guarana supplements contains various phytochemicals, including caffeine, theobromine, theophylline, tannins, saponins, catechins, epicatechins, proanthocyanidols and other compounds in minor concentrations. Guarana has been used as a stimulant since pre-Columbian times.[32] In the oncology setting, guarana is often used to decrease fatigue.

Healing touch—Healing touch (also known as therapeutic touch) is based on the belief that vital energy flows through and around the human body and may be transferred or modified. A healing touch practitioner (often a nurse trained in the practice) passes his/her hands over, or gently touches, a patient's body to balance or increase their energy. Healing touch is often used among cancer patients to improve quality of life, pain, fatigue and depression.

Hyaluronic acid cream—Hyaluronic acid cream is a topical cream containing hyaluronic acid that is used to heal wounds through repair-promoting, skin moisturizing, and potential radioprotective properties.[22] When the cream is applied, the hyaluronic acid adheres to injured tissue, provides hydration to the skin, and protects against dehydration, chemical and mechanical irritation. Hyaluronic acid cream is often used by cancer patient to prevent and treat radiation induced dermatitis.

Hypnosis—Hypnosis is facilitated by a specially trained therapist or is practiced on one's own (self-hypnosis). It is characterized by a trance-like state, which allows a patient to be more aware, focused and open to suggestion. A person in a hypnotic state can concentrate more clearly on specific feelings, thoughts, images, sensations, or behaviors without distraction.[34] The hypnotic state is obtained by first relaxing the body, then shifting attention toward a narrow range of object or ideas given by the hypnotist or hypnotherapist. A person under hypnosis may feel more calm, relaxed, and open to suggestion. In cancer patients, hypnosis is often used to help relieve stress, anxiety, and pain.

Laser therapy—Low-level laser treatment (wave lengths 650–1000 nm) has been approved in some countries, including the United States, to treat lymphedema after breast cancer surgery and is administered by trained users. Low-level laser therapy is thought to stimulate macrophages and the immune system, and break down scar tissue, thus improving lymphatic flow.[35]

Manual lymphatic drainage and compression bandaging—Manual lymphatic drainage and compression bandaging are used singly and in combination for the treatment of lymphedema following breast cancer surgery.[35] Manual lymph drainage is a specific type of therapeutic massage delivered by a health professional ideally certified in the technique. Manual lymph drainage can decrease lymphedema when administered early, before symptoms advance.[35] Compression bandages or garments, including sleeves, stockings, bras, compression shorts, gloves, bandages, or neck compression wraps, are also used to treat lymphedema and can be worn during the day or night depending on the garment and individual.[35]

Massage—There are many different forms of this form of physical therapy that involves a therapist stroking, kneading, applying friction, and stretching specific muscles and other connective tissues at an even tempo with varying levels of pressure.[36] In cancer patients, the goal of massage is to promote relaxation, address muscle stiffness and pain, and to resolve musculoskeletal complaints. There are multiple forms of massage, including but not limited to, Swedish, shiatsu, and deep tissue massage. The National Cancer Institute urges massage therapists to take precautions with all cancer patients and avoid massaging specific vulnerable areas of the body including open wounds, bruises, skin breakdown, a blood clot in a vein, a tumor site, near a medical device (e.g., drain), or sensitive skin following radiation therapy.[37, 38] In addition, certain patients with multiple bone metastases may be at risk for fracture during deep massage. The practice of massage therapy in North American is regulated by some U.S. states and Canadian provinces and territories (see Table 2).

Meditation—Meditation is a group of self-regulation practices that focus on training attention and awareness on bringing mental processes under greater voluntary control. [39] In cancer patients, these practices are intended to foster general mental well-being, calmness, clarity, and concentration. The ultimate goal of meditation varies depending on the type of practice, its history, and application. 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 judgment.[40] The focus of attention may be towards a specific target, such as on the breath, repeating a sound or mantra (known as *concentration meditation*), on all mental events that enter the field of awareness (called *mindfulness meditation)*, or a combination of both. There has been a growing interest in cancer care on the practice of a secular form of mindfulness meditation called Mindfulness-Based Stress Reduction (MBSR), based on the work of Jon Kabat-Zinn.[41] 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 of relevant concepts, discussion of progress and barriers to practice, and introduction and practice of new meditation modalities. A number of recent papers and meta-analyses have reviewed the literature on the use of MBSR in the oncology setting, some specific to breast cancer.[42–45]

Mistletoe—The use of mistletoe in cancer care is based on the premise that injections of specially prepared extracts of the plant during chemotherapy and radiation therapy can create a host response that is immune stimulatory, preferentially cytotoxic to cancer cells and protective of host cells.[46] Mistletoe is a parasitic plant from the Santalacea family that attaches to and penetrates the branches of a tree or shrub in order to absorb water and nutrients from the host plant. Use of mistletoe as a medicine extends back centuries, whereas modern use for cancer care was promoted in Europe and particularly in Germany in the early part of the 20th century.[47] There are three main types of mistletoe: European Mistletoe (*Viscum album*), Korean Mistletoe (*Viscum album var. coloratum*) and American Mistletoe (*Phoradendron leucarpum*), but multiple methods of preparation and formulation exist.

Preparations from European Mistletoe are some of the most commonly prescribed substances internationally in out-patient clinics for cancer, where it is provided most often as a subcutaneous injection or occasionally intravenously by infusion.[48] While this therapy is often used clinically for its antineoplastic potential, the clinical trial evidence on the use of mistletoe is based on trials where it is co-administered with conventional treatments to improve quality of life.[48]

Music therapy—Music therapy is the clinical use of music to accomplish individualized goals within a therapeutic relationship by a credentialed professional.[49] In cancer care, music therapy is used to address a variety of physical, emotional, cognitive, and social needs. Qualified music therapists assess patient's strengths and needs and provide indicated treatment such as creating, singing, moving to, and listening to music. Music therapy interventions can be described as either *passive* (e.g., listening to music prior to a medical intervention) or *active* (e.g., therapist instructing a patient to engage in the creation of live music) depending on the level of engagement required. Although the exact mechanisms by which music therapy works are not well understood, the most commonly accepted theories are through neurologic, psychological, behavioral and physiological pathways [50, 51] The practice of music therapy in North American is regulated by some U.S. states (see Table 2).

Reflexology—In reflexology, a trained practitioner applies pressure to the feet, hands, ears, and face with specific thumb, finger, and hand techniques with the goal of stimulating the reflex areas to promote physiological change in the body. The theory behind reflexology states that specific areas on the feet and hands correspond to specific glands, organs, and other parts of the body, which are stimulated in order to help numerous health problems.[52] Reflexology is used to cause relaxation and healing in those specific stimulated parts of the body. In oncology, reflexology is often used to promote relaxation and improve quality of life.

Relaxation techniques—A variety of techniques are employed to promote relaxation in cancer patients. The National Cancer Institute (NCI) defines relaxation techniques as including progressive muscle relaxation (PMR), guided imagery, autogenic training, biofeedback, self-hypnosis, and deep breathing exercises.[53] PMR focuses on the tightening and relaxation of specific successive muscle groups and is usually combined with breathing and imagery exercises.[54] Guided imagery can be self-directed or led by a practitioner or a recording and often involves focusing on pleasant imagery to replace negative or stressful feelings.[54] Autogenic training involves concentrating on physical sensations of warmth, heaviness, and relaxation in different parts of the body.[54] Biofeedback uses electronic devices to monitor and teach control of certain bodily functions, such as breathing or heart rate, in order to facilitate relaxation.[54] Self-hypnosis refers to the training of patients to learn to induce a hypnotic state, a natural state of aroused, attentive focal concentration along with a relative suspension of peripheral awareness, on their own or when prompted by a phrase or a cue.[54] Deep breathing exercises involve the use of slow, deep, and even breaths, sometimes called diaphragmatic or belly breathing.[54]

Qigong—The word qigong consists of two Chinese words: '*qi*' (chee) meaning life force or vital energy that flows through all things in the universe; and '*gong*' (gung) meaning accomplishment or skill that is cultivated through steady practice.[55] Qigong is a form of ancient and traditional Chinese medicine that integrates movement (physical postures), meditation (focused attention), and controlled breathing. Qigong aims to enhance vital energy or life force that balances a patient's spiritual, emotional, mental and physical health. Qigong practices are used to increase the *qi*, circulate it, use it to cleanse and heal the body, store it, or emit *qi* to help heal others. Practices range in intensity from the gentle movements of Tai Chi to the more vigorous practice of Kung Fu.[55] In cancer patients, qigong is often used to reduce anxiety, fatigue, and pain, support the immune system, and improve physical and emotional balance.

Stress management—Acute stress is a normal physical and emotional reaction that people experience as they encounter changes in life[56], including following a cancer diagnosis, during cancer treatment, and during cancer survivorship. Long-term chronic stress may contribute to or worsen a range of health problems including digestive disorders, headaches, sleep disorders, depression, anxiety, and other mental health problems.[56] To address stress and induce the relaxation response, stress management programs teach such techniques as progressive muscle relaxation (PMR), guided imagery, and breathing exercises. Stress management also typically incorporates elements of cognitive-behavioral therapy, such as understanding the effects of appraisal and perception on the experience of subjective stress.[57, 58] Participants are taught coping skills and practice various techniques for cognitive re-appraisal. One common structured group stress reduction program studied in oncology is called Cognitive Behavioral Stress Management (CBSM).[59, 60]. There are overlaps in some techniques used in stress management, relaxation, and meditation therapies. For example, meditation, guided imagery, and yoga may be practiced as techniques in isolation or combined. In this review, we distinguish between stress management, relaxation, and meditation interventions. Stress management interventions include psychoeducation on stress and coping, and emphasize cognitive-behavioral therapy and coping skills training; relaxation interventions typically consist of PMR and guided imagery; and meditation interventions use some form of meditation practice as the focal point of the training.

Soy—Soy is a plant in the pea family that has been common in Asian diets for thousands of year and more recently in the American diet.[32] Soybeans are the seeds of the soy plant and contain isoflavones and soy protein. Soy is available in dietary supplements in tablet or capsule form, and contains isoflavones and/or soy protein. Soybeans can be cooked or eaten or used to make tofu, soy milk, and other food products. Soy is also used as an additive to other processed foods such as baked goods. Soy is used to treat menopausal symptoms, osteoporosis, memory problems, high blood pressure, and high cholesterol levels.[32] In cancer patients, soy is often used to treat hot flashes.

Yoga—Yoga is a mind-body practice with origins in ancient South Asian philosophy and practice.[61] The term "yoga" is derived from the Sanskrit word *yug*, meaning "yoke" or "union".[62] This, according to traditional yoga philosophy, is the ultimate intent of a yoga

practice—to unite the individual with the totality of the universe. The techniques of yoga include ethical daily living (*yamas and niyamas*), physical postures (*asanas*), breathing techniques (*pranayama*), and meditation training (*dhyana*). There are a wide range of yoga forms and styles. The most commonly practiced form of yoga in the U.S. and Canada is Hatha yoga, which emphasizes postures *(asanas)* and often breathing exercises *(pranayama)*. In cancer patients, yoga is used for a variety of conditions, including stress, anxiety, depression, and fatigue, as well as a method to increase physical activity.

LITERATURE REVIEW ON USE OF COMPLEMENTARY AND INTEGRATIVE THERAPIES FOR CLINICAL OUTCOMES IN BREAST CANCER PATIENTS

The clinical outcomes addressed here are common symptoms and side effects that breast cancer patients experience during treatment or as sequelae of treatment. The outcomes of interest include: anxiety/stress, pain, depression/mood, fatigue, sleep disturbances, quality of life and physical functioning, CINV, radiation dermatitis, vasomotor outcomes, lymphedema, chemotherapy-induced peripheral neuropathy (CIPN), pain and sleep disturbance. Guidelines outlining conventional approaches to managing these symptoms and outcomes have been issued by national organizations such as NCCN and the American Society of Clinical Oncology (ASCO), but many of the prior guidelines and reviews have not included thorough reviews of complementary and integrative medicine approaches.[63–67] This review fills that gap for breast cancer patients.

Below, for each therapy and clinical outcome of interest that received an A or B grade, we summarize the trials that contributed to the graded recommendation in order for the reader to have an understanding of the specific interventions that were tested. To provide additional context we provide a brief review of the literature on the use of the integrative therapy for conditions other than breast cancer. We also provide a risk/benefit assessment of each therapy as well as suggestions for future research. For therapies and clinical outcomes of interest that received C, D or H grades, we provide a brief overview of the rationale for the graded recommendation. Supplemental tables provide detailed information on each trial that informed an A or B graded recommendations (Supplemental Tables 2–5). Table 3 lists the clinical outcome and integrative therapy combinations that had insufficient evidence to make an A, B, C, D or H graded recommendation.

Updated Recommendations

While the majority of graded recommendations remained the same from the previously published guidelines,[9] there are five noteworthy changes. For the outcome of anxiety and stress reduction, the use of meditation moved from grade B to grade A due to results of a fifth trial[68], in addition to the previously published four trials.[69–72], showing beneficial effects. The use of yoga for depression and mood disturbance was downgraded from grade A to grade B due to four new published studies demonstrating conflicting results.[73–76] The use of yoga for improving quality of life changed from grade C to grade B due to two added trials showing beneficial effects.[77, 78] Finally, new trials on the use of yoga[73–75, 78] and hypnosis[79, 80] for fatigue upgraded previous recommendations from grade I to grade C.

Use of Integrative Therapies for Anxiety/Stress Reduction

Description of anxiety/stress—Cancer patients may experience stress related to the life changes associated with a cancer diagnosis, both during and after treatment. Anxiety is categorized under CTCAE psychiatric disorders from grade 1 (mild symptoms and no intervention required) to grade 4 (life-threatening). Stress is often the result of life challenges that exceed the individual's perceived ability to cope, and is a common and normal reaction during cancer diagnosis and treatment. This stress is associated with symptoms of anxiety and somatic complaints that can significantly diminish quality of life.[81] Patients with anxiety may worry more frequently, have difficulty relaxing, or feel tense. Patients with cancer-related anxiety also may have elevated heart rate, myalgias, headaches, sleep disturbances, changes in appetite, nausea, diarrhea, and difficulty concentrating. The percentage of breast cancer patients reporting anxiety ranges from 12% to 47%, with approximately 11–16% of patients experiencing combined symptoms of anxiety and depression.[82–85] Evidence suggests that effective anxiety management is associated with improvements in quality of life, psychological adjustment, understanding of the disease, decision making, and adherence to treatment.[86–88]

Meditation (A grade)

Overview of meditation interventions for anxiety/stress reduction: Meditation is recommended for reducing anxiety in breast cancer patients including during radiation therapy (Grade A). Many uncontrolled trials have been published, but this recommendation is based on five RCTs completed between 2009 and 2013 that used meditation to reduce anxiety symptoms (Supplemental Table 2).[69–72, 89] Anxiety was the primary outcome for four of the trials. In all five studies, a meditation intervention was compared with a usual-care control condition. Study participants included women undergoing radiation or chemotherapy, breast cancer survivors who had completed treatment, and older adult breast cancer survivors ages 50 years and older. The study sample sizes ranged from 49 to 336 participants. Among these trials, three types of meditation interventions were tested. Three trials implemented an intensive, integrated MBSR program, customized for breast cancer patients, in which participants were trained in mindfulness meditation and gentle yoga for body awareness.[68, 71, 72] A fourth intervention was called the Mindful Movement Program and was also an intensive, integrated program, customized for breast cancer patients, that included mindful walking/moving, group discussion, exploration of body parts, specific and deliberate movements, moving with intentional effort, active energetic movement, and partner work.[69] The fifth trial assessed a Brain Wave Vibration meditation[70], or a mind/body training technique that combines simple, rhythmic movements with music, action, and positive messages.[89]

A systematic review and meta-analysis examined meditation in terms of its ability to reduce general psychological distress and stress-related health problems in adult clinical populations with a variety of health conditions; this analysis included 47 trials with 3,515 participants.[90] Overall, mindfulness meditation programs showed moderate evidence of improved anxiety at 8 weeks and at 3–6 months and showed low evidence of improved stress/distress and mental health-related quality of life. The findings of these reviews across other patient populations and disease types support our recommendations.

The earliest work in MBSR interventions specifically showed sustained benefits for individuals with anxiety disorders, and more recent research has continued to show a benefit for generalized anxiety.[91–93] The first study conducted with cancer patients, a RCT of 89 patients with a variety of cancer types, found substantial decreases in anxiety for the group receiving MBSR compared with results for a usual-care control group; results for the MBSR interventions were maintained at 6-month follow-up.[94, 95] The reduction in anxiety observed in the above trials, specifically those that used more traditional forms of MBSR, provide support for the recommendation that meditation can be beneficial for the management of anxiety in women with breast cancer.

A recent systematic review and meta-analysis of 22 studies examined the effect of mindfulness-based therapy specifically on symptoms of anxiety and depression in adult cancer patients and survivors where 21 studies included a substantial percentage or all breast cancer patients.[96] Overall, this review included 12 nonrandomized studies and RCTs. In the nonrandomized studies, mindfulness-based therapy was associated with significantly reduced symptoms of anxiety post-intervention with a moderate effect size, while the pooled effects sizes of RCTs, including the one listed above,[71] resulted in a larger effect size ($P < 0.001$). Although the review reported that overall study quality varied among studies included, there appears to be sound evidence from carefully conducted RCTs (n=9) supporting the use of mindfulness-based therapies for the management of anxiety in breast cancer patients and survivors. Another review of nine studies (including two RCTs, one quasi-experimental case-control study, and six single-group pre-post intervention studies) investigated the efficacy of MBSR on mental health specifically in breast cancer patients and found an overall decrease in anxiety scores following MBSR ($P < 0.01$).[97] This review provides further support for the use of MBSR to manage anxiety, specifically in women with breast cancer. Many other reviews reached similar conclusions, reporting positive moderate effect sizes of mind-body interventions on anxiety and distress in cancer.[45, 98]

Risk/Benefit assessment of meditation interventions: Meditation therapies pose very little risk to participants in this type of intervention. Few adverse events have been reported in any trials, but there has been recent interest within the meditation research community in exploring adverse reactions to intensive meditation practice, particularly in vulnerable individuals.[99, 100] Typically, potential participants are screened through individual orientation interviews prior to joining meditation group programs, and participants who have serious mental health issues are often re-directed to individual counseling or psychiatric intervention prior to or concomitant with mind-body intervention participation. Group facilitators are typically mental health care professionals trained to identify and manage psychological symptoms and reactions that may occur during the training.

Typically, participants in these meditation therapy groups report that the sessions are enjoyable, and dropout rates are often low and comparable to other psychosocial group programs. Because they are offered in group settings, meditation interventions are more cost-effective than traditional individual counseling or psychotherapy are and can often achieve similar results. However, the literature on meditation therapy is lacking in head-to-head comparisons with other forms of therapy, including individual counseling, cognitive-behavioral therapy, or other mind-body interventions. Hence, the specificity of meditation

therapy is not yet known. With the exception of Carlson et al.,[68] studies have not compared mindfulness-based interventions with other effective interventions. Other research suggests that the benefit is related to the degree of the participant's engagement in and commitment to the practice,[94, 101] in that participants who practice more at home often benefit more, but this area is still being investigated.[102] Drawbacks of these types of group interventions are the requirement for highly trained facilitators and the need for and ability of participants to attend in person, usually in large cities with tertiary cancer centers. In response to these issues, online and home-based adaptations of MBIs are being developed. For example, Zernicke et al.[103] demonstrated that an online live MBI group in which rural and remotely located cancer patients participated weekly over eight weeks had similar benefit to the on-site, in-person version, and patients were highly satisfied with the remote MBI adaptations.

Future research in meditation interventions for anxiety reduction: Future research on the use of meditation interventions for anxiety can similarly test novel interventions in populations who may not have ready access to in-person meditation programs.

Music therapy (B grade)

Overview of music therapy interventions for anxiety/stress reduction: *Passive* music therapy is recommended to reduce anxiety during radiation therapy, chemotherapy sessions, and post-surgery (Grade B), based upon results from five randomized clinical trials (RCTs) comparing music therapy interventions to standard care (Supplemental Table 2).[104–108] Study participants included breast cancer patients undergoing mastectomy, chemotherapy, and/or radiation therapy. The sample sizes of these studies ranged from 30 to 170 participants. The music therapy interventions were described as either *passive* or *active* music therapy, depending on the level of engagement required by the individual. Four trials examined the effect of passive music therapy, which was found to decrease anxiety scores in the intervention group[104, 105, 107, 108], including reducing sedation requirements during radiation therapy (measured as a secondary outcome).[104, 105, 107] The fifth trial, conducted by Hanser et al.,[106] examined active music therapy (which required active engagement of the participant) and yielded substantially different results from the four trials of passive music therapy. In this study, active music therapy did not result in decreases in anxiety. The discrepancy in trial results between passive and active music therapy might have occurred because the participant engagement required for active therapy does not include the potential relaxing components of passive music therapy (e.g., listening to music).

A recent systematic review and meta-analysis by Boehm et al.[109] assessed the effect of different expressive therapies, including passive and active music therapy, on improving anxiety, depression, and quality of life in breast cancer patients. The review included three of the RCTs that formed the basis for our recommendation of passive music therapy for anxiety/stress reduction, of which two trials tested passive music therapy[104, 107] and one trial tested active music therapy.[106] Another recent meta-analysis included one additional RCT evaluating art therapy.[110] Boehm et al. found a clinically and statistically significant mean difference ($P < 0.01$) in the anxiety scores of patients receiving music therapy compared to the control group,[109] thus further supporting our recommendation of passive music therapy for reducing anxiety. Passive music therapy has also been shown to reduce anxiety among

patients undergoing mammographic screening indicating that the recommendation may apply broadly to an adult women in a clinical cancer setting.[111]

Risk/benefit assessment of music therapy: Passive music therapy is noninvasive, does not interfere with a patient's privacy, and has no reported deleterious effects. Furthermore, it does not require costly, technologically advanced equipment and can be implemented in a variety of locations. As such, passive music therapy can be safely and effectively implemented in clinical settings with breast cancer patients to help reduce short-term anxiety associated with receiving medical care for their cancer.

Future research in music therapy for anxiety reduction: Future research should assess long-term effects of passive music therapy on anxiety, as the trials reviewed here only assessed short-term reductions in anxiety. Although active music therapy may also have benefit, more than one existing trial will be needed for a comprehensive risk/benefit assessment. Trials that directly compare the effect of passive music therapy and active music therapy on anxiety are needed to clarify whether benefit is due to listening to music in a relaxed state or participating in the creation of music.

Stress Management (B grade)

Overview of stress management interventions for anxiety/stress reduction: Stress management is recommended to reduce anxiety in patients during breast cancer treatment, (Grade B) but long-term stress management group programs appear to be better than self-administered home programs. This recommendation is based on four RCTs completed in 2008–2013 with breast cancer patients that tested a stress management intervention compared with usual care in improving anxiety as the primary outcome.[112–115] Study participants included only breast cancer patients in two[112, 115] of the four trials and mixed cancer patients with a significant proportion of breast cancer patients in the other two.[113, 114] For all four trials, breast cancer patients were included from defined periods along the continuum of care, including pre-surgery, during chemotherapy, and after cancer treatment. Patients were thus either undergoing or had undergone surgery, chemotherapy, or radiation therapy, either alone or in combination. The study sample sizes for these trials ranged from 85 to 286 participants. Of the four trials, two studies found that the improvement was statistically significantly different compared to the control group.[113, 115] One trial found similar improvement in both the intervention and control group with no statistically significant differences across groups, [112] while the fourth trial found no improvement. [114] (see Supplemental Table 2, Stress Management).

Stress management interventions varied among the studies (Supplemental Table 2).[112–115] One trial[112] implemented a self-administered stress management intervention before receiving chemotherapy. The intervention included video and booklet information specific to stress management and exercise and was delivered by a doctoral level psychologist.[112] A second trial[112] offered stress management modalities that included guided imagery techniques, relaxation, meditative exercises, and counseling that aimed to promote active coping, alert relaxation, and a positive attitude toward change. Instruction was given in person and was complemented by audio CDs for use at home. Face-to-face sessions lasted

45–60 minutes each and took place in the hospital.[112] The stress management portion included information, demonstrations and instructions for paced breathing, progressive muscle relaxation with guided imagery, and use of coping strategies to manage stress. A third trial[113], a multi-center community clinical oncology program involving 20 clinical sites, was designed to determine whether a self-administered stress management intervention, previously found to be beneficial to cancer patients, would improve quality of life and decrease psychological distress (including anxiety and depression) in patients receiving chemotherapy at community clinical centers. The study used a factorial design to test stress management training, exercise training, the combination of stress management and exercise training, and usual care. Patients assigned to stress management training were provided written materials and videos on three techniques, including progressive muscle relaxation and guided imagery, abdominal breathing, and coping skills training. [113] A fourth trial[115] examined the effects of a cognitive behavioral stress management intervention (comprised of relaxation training including meditation, guided imagery, PMR, and breathing techniques, cognitive restructuring, and coping skills training) on late-afternoon serum cortisol and relaxation indicators in women undergoing treatment for non-metastatic breast cancer.

A systematic review by Trijsburg et al. evaluated the effects of stress management techniques on mental health outcomes, including anxiety, across 22 studies using samples of heterogeneous cancer populations that included six studies of breast cancer-only samples.[116] The interventions assessed were all structured and included counseling and coping components in addition to some interventions including progressive muscle relaxation, guided imagery, self-hypnosis, and deep breathing. Overall, the review found positive effects for mental health outcomes, including anxiety scores.

Risk/benefit assessment of stress management interventions: Stress management therapy is noninvasive, nontoxic, and has no appreciable risk to patients. Stress management does not require specialized equipment and can be implemented in a variety of locations. Resources for providing instruction on self-management practices are broadly available. As the majority of the trials discussed above tested long-term interventions, the guideline recommendation is specific to long-term stress management programs. This may, however, be complicated by other factors, including the potential increase to the cost of delivery for providers/facilitators as a result of the implementation of longer term programs and could also present a barrier to patients with access-to-care and other health care disparity issues. Overall, it is recommended that stress management therapy can be safely and effectively implemented in clinical settings for breast cancer patients.

Future research in stress management interventions for anxiety reduction: Future research in this area should compare in-person, professionally led stress management group programs to home-based self-study and internet-based stress management intervention options that are less costly and more broadly accessible. Research should also examine long-term outcomes of each type of delivery modality.

Yoga (B grade)

Overview of yoga interventions for anxiety/stress reduction: Yoga is recommended for reducing anxiety in breast cancer patients (Grade B). This recommendation is based on nine RCTs, completed between 2007 and 2014, in which a yoga intervention was implemented to reduce physical symptoms and psychological distress, including anxiety, which assessed as the primary outcome in four of the studies (Supplemental Table 2).[75, 117–124] These nine trials tested five different yoga interventions. The first intervention was an intensive, integrated yoga program, customized for breast cancer patients, in which participants were led through slow stretching and loosening exercises, various postures (*asanas*), guided imagery specific to cancer, positive thought provocation, chanting exercises, various breathing exercises (*pranayama*), and soothing sound vibrations and guided imagery (*yoga nidra*).[117–120] A second intervention implemented *Iyengar* yoga, a traditional form of Hatha yoga that emphasizes postures and breathing techniques that target symptom-specific concerns using passive inversions (upside-down postures with the head lower than the heart) and passive backbends (supported spinal extensions).[121] A third intervention used Patanjali's Yoga Sutras that included warm-up movements synchronized with breathing, selected postures, deep relaxation techniques, alternate-nostril breathing (*pranayama*), and meditation.[124] The fourth intervention implemented meditation and breathing exercises that focused attention on internal body sensations, as well as yoga exercises (modified *asanas*) composed of gentle stretching and strengthening exercises.[75] *Pranayama* or yoga breathing practices was tested in the remaining trials. [122, 123] Study participants included women who had been recently diagnosed with breast cancer, those who were currently undergoing radiation or chemotherapy or a combination of both, and those who were experiencing significant fatigue post treatment. The study sample sizes ranged from 23 to 98 participants.

Several recent reviews of yoga interventions for individuals with cancer have been published.[125–128] The first meta-analysis investigating the impact of yoga interventions on psychological health outcomes[129] identified 10 articles that examined outcomes in breast cancer patients (n=7 articles), lymphoma patients (n=1), and mixed cancer populations (n=2). Analyses involving eight trials that assessed anxiety found lower anxiety associated with the yoga groups relative to controls ($P = 0.009$); similar results with yoga interventions were observed for distress ($P = 0.003$) and stress ($P = 0.006$). However, since this was a heterogeneous sample of patients, it was unclear whether the results could be generalized specifically to breast cancer patients. More recently, a systematic review and meta-analysis assessing the impact of yoga interventions on quality of life and psychological health specifically in breast cancer patients and survivors was conducted.[130] Overall, 12 randomized clinical trials were included in the analysis with a total of 742 participants. Analyses revealed short-term positive effects of yoga interventions on improved psychological health, including anxiety ($P < 0.01$), perceived stress ($P = 0.03$), and psychological distress ($P < 0.01$). It is, however, notable that these effects were applicable only to those who engaged in yoga during active cancer treatment and not in the post-treatment period. The authors state that based on these positive preliminary results, a wide variety of yoga practices could be recommended for this population.[130] Finally, although the methodological quality across the trials is variable, yoga has been shown to be beneficial for

reducing psychological distress in a wide variety of non-cancer clinical populations, including adult patients with anxiety and depression.[131, 132]

Risk/Benefit assessment of yoga interventions: Yoga interventions are noninvasive and with proper instruction can be adapted to people with functional and other impairments without harm. Yoga interventions are low cost and can be practiced at home with instructional videos but in the context of breast cancer are best undertaken under the guidance of certified yoga instructors with specific training in teaching cancer patients and survivors. Such programs also have the ability to be adapted and modified for people with medical conditions or limited mobility.[133] Older adults, individuals with limited mobility, and those with chronic medical conditions should proceed with yoga therapy only under the guidance of a certified instructor to minimize potential risk of harms such as strained muscles and dizziness if yoga postures are attempted incorrectly or prematurely.

Future research in yoga interventions for anxiety reduction: Many of the studies investigating the impact of yoga on psychological outcomes in individuals with cancer should be interpreted with caution given that many of these studies are small and preliminary. Furthermore, the studies summarized above have some inconsistency of results; the trials from India[117–120] reported consistently positive results while the trials from North America[75, 121–124] reported less consistent positive results. Nevertheless, many of the studies and reviews that examined yoga interventions reported overall positive outcomes in several physical, psychological, and quality of life measures. Future trials of yoga interventions for anxiety/stress reduction should focus on testing forms of yoga that can be more easily applied, and in order to improve the generalizability of the results, test the interventions in larger sample size and in minority and underserved populations who may not have easy access to yoga programs.

C graded therapies for anxiety and stress reduction—Acupuncture[134–136], massage[137–140] and relaxation[141–145] can be considered for use for anxiety and stress reduction (Grades C). Three high-quality trials assessed acupuncture for anxiety and stress reduction, which were secondary outcomes. Two of the three positive trials were small[134, 135] and one trial showed no effect[134]. Four studies examined massage for anxiety, however, three studies with positive findings included fewer than 40 participants[137–139] and one study found no effect[137]. Results were inconclusive regarding relaxation for anxiety and stress reduction due to inconsistent results and small sample sizes. Future directions in research can focus on assessing these modalities in a large high-quality trial assessing anxiety as the primary outcome.

Use of Integrative Therapies for Depression/Mood Disturbances

Description of depression/mood disturbances—Both during and after cancer therapy, patients may experience symptoms of depression, as they often feel a sense of loss of health and the life they had before their cancer diagnosis.[81] The CTCAE categorizes depression as a psychiatric disorder on a scale of 1 (mild) to 5 (death). Symptoms of depression in cancer patients may include persistent feelings of sadness, numbness, nervousness, guilt, worthlessness, helplessness or hopelessness, difficulty concentrating or

behavior that includes being short-tempered or moody, crying for long periods of time or many times each day, lacking interest or pleasure in performing activities, and having suicidal thoughts. Other symptoms may include weight change, sleep disturbances, tachycardia, dry mouth, increased perspiration, gastrointestinal symptoms, diarrhea, changes in energy level, persistent fatigue, headaches, or myalgias. The percentage of breast cancer patients reporting depression ranges from 3% to 34% and 11–16% of patients experienced combined depression and anxiety symptoms, depending on the population studied.[82–85] Effectively managing depression may improve quality of life, psychological adjustment, understanding of the disease, decision making, adherence with cancer treatment, and response to cancer treatment.[86–88]

Music therapy (B grade)

Overview of music therapy interventions: Passive music therapy is recommended to improve depression/mood disturbances in newly diagnosed breast cancer patients (Grade B). This recommendation is based on four RCTs completed between 200 and 2011 that tested a music therapy intervention to improve mood/depression (Supplemental Table 3).[106, 108, 146, 147] Depression/mood disturbances was assessed as either the primary outcome or secondary outcome to anxiety. In all four trials, a music therapy intervention group was compared with either a waitlist or a standard care control group. Study participants included women with a breast cancer diagnosis who had completed mastectomy, chemotherapy, or radiation therapy or who had metastatic disease. The study sample sizes ranged from 8 to 170 participants. Three trials examined the effect of passive music therapy, which was found to decrease depression scores compared to control [108, 146, 148], while the fourth trial examining active music therapy [106] yielded no clinically meaningful long-term effects between groups or over time. Active music therapy resulted in immediate effects on happiness within the intervention group, which was not sustained over time. Therefore, the guideline recommendation is specific to passive music therapy.

Out of five studies combined in the meta-analysis described above that assessed multiple types of art therapies for improving anxiety, depression, and quality of life among breast cancer patients[109] (four music therapy interventions including two trials identified in our review[106, 110], and one art therapy trial), a clinically and statistically significant mean difference ($P = 0.05$) was found across all depression scores in the music therapy intervention groups compared with control groups. Further, a systematic review of music therapy specifically for depression in the Cochrane Database of Systematic Reviews found that although only five RCTs have tested music therapy interventions for depression and met the review study inclusion criteria, this therapy is widely accepted and beneficial to a broad range of individuals with depression and is associated with improvements in mood disturbances.[149] Taken together, this literature supports our recommendation of passive music therapy for reducing depression and improving mood.

Risk/benefit assessment of music therapy interventions: The risk/benefit assessment of passive and active music therapy interventions for depression/mood among breast cancer patients is the same as for anxiety depression (see above).

Future research in music therapy interventions for depression/mood: Future research in this area should assess long-term effects of passive music therapy on mood disturbances/depression because the reviewed trials are limited to assessing short-term improvement of mood/depression following breast cancer treatments or during metastatic cancer diagnosis. In addition, studies should attempt to replicate the null findings of active music therapy interventions in order to formulate a comprehensive risk/assessment regarding active music therapy. Suggestions for future research in music therapy for improving depression/mood are similar to those for anxiety, as stated in the anxiety section above.

Yoga (B grade)

Overview of yoga interventions for depression/mood disturbances: Yoga is recommended for improving mood disturbances and depressive symptoms in women with breast cancer (Grade B). This recommendation is based on the results of 15 RCTs completed between 2006 and 2015 that employed a yoga intervention to reduce physical symptoms and psychological distress, including depression (Supplemental Table 3).[73–76, 117–119, 121–124, 150–153] Depression or depressive symptoms were the primary or secondary outcome for all studies included in this review. Study participants included women recently diagnosed with or having a recurrence of breast cancer; women who were undergoing radiation therapy, chemotherapy, or a combination of both; an ethnically diverse and underserved sample of female patients, and women who had completed breast cancer treatment. Five different yoga interventions were tested in study samples ranging from 23 to 200 participants. Five trials assessed an intensive, integrated yoga program, customized for breast cancer patients, including *asanas*, *pranayama*, and *yoga nidra*.[76, 117, 118, 153, 154] Five trials implemented *Iyengar* yoga, a traditional form of Hatha yoga, and passive backbends.[74, 121, 150–152] Two trials assessed Patanjali's Yoga Sutras that included warm-up movements synchronized with breathing, selected postures, deep relaxation techniques, meditation, and alternate-nostril breathing (*Pranayama*),[73, 124] while two trials evaluated only the *Pranayama* practices.[122, 123] Finally, a yoga exercise intervention implemented meditation and breathing exercises that focused attention on internal body sensations, as well as yoga exercises (modified *asanas*) composed of gentle stretching and strengthening exercises.[75]

Yoga has been shown to be beneficial for reducing depression in a wide variety of clinical populations.[132, 155–157] and specifically for individuals with cancer.[125–128] One meta-analysis investigating the impact of yoga interventions on psychological health outcomes[129] analyzed eight trials of yoga interventions for depression and showed improvement in depressive symptoms in the yoga groups when compared with patients in the control groups ($P = 0.002$) among a heterogeneous sample of patients. Specifically in breast patients and survivors, a meta-analysis[130] of 12 RCTs, representing a total of 742 participants, revealed short-term effects of yoga interventions on improved psychological health, including depression ($P < 0.01$). A caveat was that the observed efficacy was only applicable for yoga practiced during active cancer treatment and not necessarily in the post-treatment period. Overall, the authors state that based on these positive preliminary results, yoga therapy should be used in this population.

Risk/benefit assessment of yoga interventions: The risk/benefit assessment of the effects of yoga on depression and mood disturbance outcomes is similar to the assessment for anxiety outcomes. Studies assessing yoga for psychological outcomes in individuals with cancer are typically small, not well controlled, and preliminary in nature. Furthermore, comparability across studies is difficult as findings differ between populations from India[117–119, 153] and North America.[121, 122, 150–152, 158] Despite these limitations, the evidence suggests that yoga interventions could be added to treatment plans or added in the post-treatment period, provided these interventions are facilitated by appropriately trained yoga instructors and can be adapted and modified for people with medical conditions or limited mobility.[133]

Future research in yoga interventions for depression/mood: Future trials of yoga interventions to improve mood disturbances/depression should test the effects of different types, doses and durations of yoga on patient populations with varying degrees and types of mood disturbances and depression in addition to including larger sample sizes and testing across active controls.

Meditation (A grade)

Overview of meditation interventions for depression/mood disturbances: Meditation, particularly MBSR, is recommended for treating mood disturbance and depressive symptoms in breast cancer patients (Grade A). This recommendation is based on 10 RCTs, completed between 2009 and 2015 that used meditation to help reduce depressive symptoms (Supplemental Table 3).[68–72, 159–162] Depression was the primary or secondary outcome for all of the trials. In eight[69–72, 159–161] of the 10 trials, a meditation intervention was compared with a usual care group, a waitlist control, or another active intervention; two other trials used a three-arm trial design.[68, 162] Study participants included women undergoing current radiation therapy or chemotherapy for breast cancer, breast cancer survivors who had completed treatment, and adult breast cancer survivors 55 years and older. The study sample sizes ranged from 33 to 336 participants and tested six different types of meditation interventions, including an intensive, integrated MBSR program customized for breast cancer patients[68, 71, 72, 160, 162], the Mindful Movement Program[69], Brain Wave Vibration meditation[70], Tibetan sound meditation[159], Cognitively-Based Compassion Training[163], and Transcendental Meditation[161].

In the meta-analysis examining the effect of mindfulness-based therapy on psychological outcomes in adult cancer populations,[96] compared with results in controls, mindfulness-based therapy was associated with significantly reduced depression post-intervention, with a moderate effect size in the nonrandomized studies and the RCTs, including one trial listed above[71] ($P < 0.001$). Using evidence from nine well-conducted studies, the review and meta-analysis by Zainal et al. confirms the use of mindfulness-based therapies for the management of depression in breast cancer patients and survivors despite the heterogeneity in the reviewed studies. The results of the meta-analysis found a significant pooled effect size for MBSR on depression scores (effect size = 0.575; 95% CI = 0.429, 0.722; $P < 0.01$).[97] In their study, Teasdale et al.[164] modified traditional MBSR by combining it with principles of cognitive behavioral therapy (CBT) to create mindfulness-based cognitive

therapy (MBCT), which was designed specifically to prevent recurrence of depressive symptoms in individuals with relapsed major depression.[165] The intervention proved effective for preventing depression relapse[164] in a sample of >75% women with cancer (though type of cancer is not specified), and has since been widely applied and adapted to treat depression symptoms in a range of clinical samples.[166] In cancer patients, other RCTs of meditative interventions showed decreasing depressive symptoms,[94] with results maintained after 6-months' follow-up.[95] The reduction in depressive symptoms observed in the above trials comprising these reviews and meta-analyses provide further support for the recommendation that meditation can be beneficial for the management of depressive symptoms in women with breast cancer.

Risk/benefit assessment of meditation interventions: The risk/benefit assessment of the effects of meditation intervention on depression and mood disturbance outcomes is similar to the assessment of anxiety outcome. Despite these limitations, the evidence suggests that meditation and MBSR could be added to treatment plans or added in the post-treatment period, provided that these interventions are facilitated by appropriately trained instructors and can be adapted and modified if needed for individuals with cancer.

Future research in meditation interventions for depression/mood: Future research on meditation interventions to improve mood disturbances/depression should focus on understanding the type, duration and lasting effect of specific meditation techniques on specific mental health outcomes.

Massage (B Grade)

Overview of massage therapy interventions for depression/mood disturbances: Massage therapy is recommended to improve mood disturbance in breast cancer survivors following active treatment (i.e., surgery, chemotherapy, radiation) (Grade B). This recommendation is based on results from six trials completed between 2004 and 2012. [138–140, 167–169] In the trial reported by Listing et al.,[168] the primary outcomes focused on physical discomfort and fatigue, with mood disturbance being a secondary outcome. The other five trials assessed depression as the primary outcome and had other secondary outcomes, including perceived stress, quality of life, pain, heart rate variability, and emesis. In the five trials, the effect of massage therapy was compared with the effect of standard care. The studies, which took place in the United States,[138] Germany[139, 167, 168], England[140], and Spain,[169] all included breast cancer survivors who had completed active cancer treatment at least three months prior to study enrollment. The study sample sizes ranged from 20 to 288 participants. In three of the six trials, the massage therapy intervention was a variation of classic massage involving rhythmic stroking, kneading, and acupressure at select areas on the body. [139, 167, 168] The study of Fernandez-Lao used an experienced and trained physical therapist to administer manual massage therapy.[169] Wilkinson et al.[140] included aromatherapy as part of the massage therapy, which was individualized across study participants. Hernandez-Reif et al.[138] combined massage with acupressure and Trager®, which uses hundreds of small, rocking and elongating movements that release muscle tension. The number and frequency of massage therapy sessions varied across the studies.

All of the trials assessing classic massage therapy used the same protocol of bi-weekly, 30-minute massages for five weeks[139, 167, 168] with the exception of the Fernandez-Lao et al. trial, which assessed a one-time 40-minute massage session.[169] Across these studies, compared with control groups, women in the intervention group reported significant improvement in mental health outcomes, including reduced depression and mood disturbance scores particularly in relation to anxious depression, anger, and tiredness. These differences between groups, however, were not consistently sustained across all studies. For example, in the study of Fernandez-Lao et al., the improvements in depression outcomes with one-session massage intervention depended on the participant's individual level of enthusiasm for that intervention. The classic massage studies[139, 167, 168] and one trial with massage combined with aromatherapy[140] found that the massage interventions significantly decreases depression only immediately following the intervention but not long term. The remaining study that combined massage therapy with acupressure and Trager®[138] demonstrated a positive effect of the interventions on anxiety and depression with these effects sustained at long term follow-up.

A systematic review and meta-analysis examined the role of massage interventions in the management of treatment-related side effects associated with breast cancer in terms of improvement in overall quality of life, including measures of depression.[170] A total of 18 RCTs were included in this review. Overall regular massage therapy was shown to have positive effects on other outcomes such as anger and fatigue symptoms, but the meta-analysis of eight trials, three of which were summarized in this section,[138, 139, 168] did not find significant beneficial effects of massage therapy for depression. This meta-analysis, however, was limited by significant heterogeneity across the studies assessing depression as the outcome ($P = 0.002$) as well as by small and possibly underpowered sample sizes that may have accounted for the non-significant results. An earlier systematic review of massage therapy in breast cancer populations that found no positive effect of massage on depression also concluded that few rigorous trials have been conducted and that the risk of bias in such trials is high.[171]

Risk/benefit assessment of massage therapy interventions: Classic massage is a non-invasive therapy that has limited adverse effects. For cancer patients, massage therapy by a trained massage professional appears to have few risks and may reduce pain, promote relaxation, and boost mood, at least in the short term.[172] Since trained, licensed therapists delivered the interventions tested in these studies, the recommendation of massage for depression applies specifically to massage by trained therapists.[173, 174] Some caution is needed, however, for individuals receiving anti-coagulation therapy due to their risk of bruising. Women with breast cancer who have undergone radiation therapy or surgery or have implanted medical devices also may need to be cautious in having massage to the affected regions. In addition, some women may be reluctant to disrobe due to altered body image, modesty, or ethnocultural issues. Thus, important considerations include appropriate draping of the individual and ensuring that the massage therapist is sensitive to the treatment experiences of women with breast cancer and develops a therapeutic relationship with the individual. Ensuring that the massage therapist is the same gender as the patient is considered best practice in the massage profession and may also increase an individual's

comfort with receiving massage therapy. However, this practice was not tested in the studies included in this review.

Future research in massage interventions for depression/mood: A 2008 systematic review of massage therapy for depression in the general public concluded that evidence to support massage as an effective treatment for this indication and population was lacking.[175] However, a more recent (2010) meta-analysis of 17 RCTs concluded that massage therapy had a positive effect on individuals suffering from depression.[176] That meta-analysis also highlighted the heterogeneity across massage therapy trials in terms of therapy protocols, outcomes measurement, and populations and underscored the need for standardization across future massage therapy trials. These issues are also true for the trials assessing massage interventions for depression/mood in breast cancer patients. Future research on massage therapy interventions to improve depression/mood disturbances should focus on understanding how best to disseminate cost-effective massage interventions in routine clinical settings.

Relaxation (A grade)

Overview of relaxation interventions for depression/mood disturbances: Relaxation therapy is recommended for improving mood disturbances and depressive symptoms when added to standard care (Grade A). The recommendation put forth in the guidelines is based on results from six RCTs, completed between 1999 and 2007, which implemented a relaxation program with or without guided imagery as an intervention to improve mood disturbances and treat depression (Supplemental Table 3).[141, 144, 145, 177–179] Five of the six trials measured depression as the primary outcome. In all six trials, a relaxation therapy intervention group was compared with a standard care group. The interventions comprised some form of relaxation therapy that included progressive muscle relaxation and guided imagery or visualization techniques. One trial[141] assessed autogenic training that provided training in relaxation that is meant to induce heaviness and warmth of limbs, calming of the heart and breathing, abdominal warmth, and cooling of the forehead. Limitations of all of these trials included the potential for expectation bias attributable to the inability to blind participants and a lack of attention control groups, although one study used a health education attention control.[179] Participants in these studies included breast cancer patients who had or were currently undergoing surgery, chemotherapy, or radiation therapy. The study sample sizes ranged from 31 to 183 participants.

The majority of pertinent systematic reviews combine relaxation techniques with stress management, psychosocial, and psychological interventions for breast cancer patients. Thus, a review specific to relaxation interventions that includes progressive muscle relaxation and guided imagery for depression/mood or other psychological outcomes in breast cancer patients and survivors is warranted. A review study of guided imagery as adjuvant cancer therapy broadly assessed six RCTs and found the methodological quality inconsistent.[180] Across trials, the results provided few details, and the studies were implemented with heterogeneous cancer populations, interventions, and outcome measures, which ultimately precluded statistical pooling of the results. Despite these limitations, guided imagery as a

sole adjuvant cancer therapy was found to be supportive and to increase comfort in patients with few risks.

Beyond decreasing depression, relaxation therapy may also have a beneficial impact on other symptoms important to women with breast cancer. For instance, progressive muscle relaxation has been found effective at ameliorating sleep problems and fatigue in women undergoing chemotherapy for breast cancer.[181] Other likely benefits attributable to this therapy in this breast cancer population include reduced nausea and anxiety.[182–185]

Risk/benefit assessment of relaxation interventions: Relaxation therapy is non-invasive and positively engages the patient with very little potential for harm. The goal of this treatment approach is to use principles of psychoneuroimmunology to better regulate the hypothalamic pituitary-adrenal axis, modulate cortisol production, and decrease stress, which may have other health benefits including psychological outcomes that may be affected by stress and distress (such as anxiety and depression/mood disturbances). Some of the appeal of relaxation therapy includes its low cost, safety, and portability. With adequate training, patients themselves can apply this therapy when and where they want without the need for supervision. However, the durability of relaxation therapy and the frequency required to sustain a long-term positive effect on depression remain unclear. It seems that relaxation therapy is not only applicable for those with breast cancer and depression but also has been shown to be beneficial in other contexts, including to decrease depression in adults[186, 187] and depression associated with cardiac disease.[188] The minimal cost and low potential for harm with relaxation therapy in conjunction with its evidence of benefit supports its A grade recommendation for depression.

Future research in relaxation interventions for depression/mood: In addition to the gaps in the literature described above, future research on the use of relaxation interventions to improve mood disturbances should focus on how to use novel electronic communication strategies to deliver low-cost relaxation techniques to diverse patient populations.

C graded therapies for depression/mood—As trials have been conducted on the effects of acupuncture[134–136, 189, 190], healing touch[191, 192], and stress management[112–114, 193, 194] on depression and improvement in mood, these therapies can be considered (Grades C). Five trials assessed acupuncture as a treatment for depression/mood (but as a secondary outcome) and only one trial was large, [136] with mixed findings in terms of effect. Two studies assessed the effect of healing touch on depression as a primary outcome, with one small study showing no effect[191] and a larger study showing a positive effect[192]. Though five large studies were reviewed for the effect of stress management on depression/mood, findings were inconclusive due to inconsistent results across trials. Future research directions include conducting trials with larger samples sizes and replicating trials with these modalities to examine impact on depression symptoms and improving mood as the primary outcome.

Use of Integrative Therapies for Fatigue

Description of fatigue—Among cancer patients, fatigue is commonly referred to as cancer-related fatigue. Fatigue is a multi-factorial condition marked by extreme tiredness and inability to function due to lack of energy.[195] According to National Comprehensive Cancer Network (NCCN) guidelines, ratings of fatigue of 4 or higher on a scale of 0 to 10 (where 10 is very severe fatigue) are further evaluated for known contributing factors such as pain, emotional distress, anemia, sleep, nutrition, and level of activity. These comorbidities are then treated. The CTCAE measures fatigue from grade 1 (relieved by rest) to grade 3 (not relieved by rest, limiting activities of daily living). Fatigue is the most frequent and distressing side effect of common antineoplastic therapies, including chemotherapy, radiation therapy, surgery, and selected biologic response modifiers.[196] Although cancer-related fatigue typically improves upon the conclusion of treatment, it can last for months or years in up to one-third of patients and become a chronic condition that leads to a variety of physical and psychological effects long into survivorship. Symptoms of fatigue include feeling tired, weak, worn-out, heavy, slow, or having “no energy or get-up-and-go”. Cancer-related fatigue is different from common tiredness in both its magnitude and quality. Cancer-related fatigue is not typically relieved by rest and is much more profound than simply feeling tired. About 33% of patients with breast cancer experience moderate to severe fatigue. [197–199] Fatigue has disruptive consequences and can have a negative impact on a patient’s quality of life, mood, and self-esteem.[64] Cancer-related fatigue can prevent patients from taking part in daily activities, relationships, social events, community activities, as well as work or school, which can have financial consequences, such as loss of employment and health insurance.[64]

C and D graded therapies for fatigue—There are no A or B graded therapies to report for fatigue. Trials evaluating hypnosis [79, 80], Acetyl-L-carnitine[200], and guarana[201, 202] have examined their effects on fatigue during treatment as a primary outcome. Two trials from a single research group reported beneficial effects of hypnosis on fatigue during treatment, therefore hypnosis can be considered for use for fatigue during treatment (Grade C). Neither Acetyl-L-carnitine nor guarana are recommended for improving fatigue during treatment due to a lack of effect in clinical trials among cancer patients (Grades D). Ginseng received a Grade C for fatigue during treatment based upon a single high quality trial with a large sample size.[203] A previous large, high quality dose finding study by the same group indicated that a higher dose was more effective.[204] In subset analyses in the subsequent trial, which tested use in patients reporting fatigue either during or after treatment, results showed that ginseng was more effective in patients undergoing active treatment. Trials testing the effects of acupuncture[136, 205–207] and yoga[73, 74, 78, 121, 152, 208, 209] for post treatment fatigue yielded modest results, suggesting that these therapies can be considered for use (Grades C). Four high quality acupuncture trials assessed fatigue as the primary outcome; three of the four trials included a large sample size.[136, 205–207] Acupuncture for post treatment fatigue received a C grade mainly due to inconsistent comparison groups across the trials, including sham acupuncture,[205, 207] standard of care,[136, 206] self-administered acupuncture,[206] and wait-list control.[207] Six trials evaluated yoga for post treatment fatigue as a secondary outcome only;[73, 74, 78, 121, 152, 208, 209] only two studies had a large sample size[73, 74] where each reported contrasting results.

Use of Integrative Therapies for Quality of Life/Physical Functioning

Description of quality of life and physical functioning—Quality of life is a multi-dimensional construct typically measuring the functioning of emotional, physical, role, and social domains using validated questionnaires.[210] The majority of breast cancer patients report some level of diminished quality of life during cancer treatment and/or survivorship.[211] The physical domain includes common physical side effects of cancer and cancer treatment, including constipation and diarrhea, fatigue, hair loss, fever, hot flashes and night sweats, lymphedema, nausea and vomiting, poor nutrition, oral complications, pain, and skin changes, as well as the ability to function physically in everyday life. The emotional domain includes psychological functioning with indicators of anxiety, depression, distress, confusion, and memory problems. The sexual functioning domain refers to patients' perception of sexuality and sexual functioning, attractiveness, and fertility. Finally, the social domain refers to the patients' social functioning, their social role, and level of social support. Each of the domains, either individually or in combination, influences a patient's quality of life.[212–214] Decrements in quality of life may persist upon the conclusion of treatment, on chronic/long-term hormonal and biotherapies and into survivorship.[215]

Meditation (A grade)

Overview of meditation interventions for quality of life/physical functioning: Meditation is recommended for improving quality of life in breast cancer patients (Grade A). This recommendation is based on seven RCTs, completed between 2009 and 2013, which used meditation for this indication (Supplemental Table 4).[69–71, 160–162, 216] Quality of life was the primary outcome in four of the seven trials.[160–162, 216] In four trials, a meditation intervention group was compared with a usual care or waitlist control condition group, and three other trials[160, 162, 216] used a three-arm design. Study participants included women undergoing radiation therapy for breast cancer, newly diagnosed breast cancer patients of stages 0-IV, breast cancer survivors who had completed treatment, and older adult breast cancer survivors aged 55 years and older. The study sample sizes ranged from 47 to 180 participants. These trials overlap with the trials described under meditation intervention for anxiety and depression outcomes (see above). Of these trials, four trials tested an intensive, integrated MBSR program customized for breast cancer patients where two studies included women post-surgery, radiation or chemotherapy treatments,[118, 152,] one study included women during radiation therapy[154], and one study included recently diagnosed patients.[71, 160, 162, 216] One trial assessed the Mindful Movement Program, also an intensive, integrated program for breast cancer patients[69], in addition to a trial assessing Brain Wave Vibration meditation[70] and Transcendental Meditation[161] for improvements in quality of life scores.

Previous research has supported the role of MBSR interventions for improved quality of life in heterogeneous samples of cancer patients and survivors, with effect sizes ranging from small to large on quality of life scales.[101, 217, 218] One review in particular assessed the impact of MBSR on quality of life in breast cancer patients.[45] In that review, the authors identified only three studies that met their criteria and also measured quality of life as an outcome.[71, 216, 219] Of the three studies that measured quality of life, only one study (also included in our review) reported significant improvements post-MBSR intervention[71]

relative to results in control or comparator groups. The other two trials reported no significant improvements in quality of life after MBSR intervention or at follow-up. A second systematic review and meta-analysis was conducted to investigate the effect of MBSR in the cancer care setting on several psychological outcomes, including quality of life.[98] The analyses specific to the quality of life outcome included 248 patients in six studies and reported a small effect size ($P < 0.01$). The authors suggest that although these findings support the use of MBSR for improving quality of life, more well-conducted RCTs are required that implement adequate controls, longer follow-up periods, larger samples sizes, and obtainment of patients' psychological profiles.

Risk/benefit assessment of meditation interventions: There is very little risk to participants who use meditation therapies to improve quality of life and/or physical functioning. Few adverse events have been reported in any trials involving meditation, with participants typically reporting positive feedback about meditation, resulting in low dropout rates from the programs. Group meditation formats and online and home-based adaptations of MBIs[103] are cost-effective and beneficial therapies that can be used as adjuncts to traditional individual counseling or psychotherapy.

Future research in meditation interventions for quality of life/physical functioning: To improve specificity of the effective components of meditation and to compare meditation interventions to other mind-body interventions, research assessing meditation as a treatment for improved quality of life and/or physical functioning should be extended to directly compare meditation with other forms of therapy, including individual counseling, cognitive behavioral therapy, and other mind-body interventions, similar to the therapies compared in the trial by Carlson et al.[68]

Yoga (B grade)

Overview of yoga interventions for quality of life/physical functioning: Yoga is recommended for improving the quality of life in breast cancer patients (Grade B). This recommendation is based on 12 RCTs, completed between 2006 and 2015, which tested a variety of yoga programs (Supplemental Table 4).[77, 78, 119, 122, 124, 150–153, 208, 209, 220] Quality of life was the primary outcome for six of the 12 trials.[77, 150, 151, 208, 209, 220] In 10 trials, a yoga intervention group was compared with a usual care or waitlist control condition group, and two others used brief supportive therapy as a comparison group.[154, 221] Study participants included women undergoing radiation therapy or chemotherapy for breast cancer, newly diagnosed breast cancer patients, and breast cancer survivors who had completed treatment. The study sample sizes ranged from 15 to 128 participants. Several of these trials overlap with those described under yoga interventions for anxiety and depression outcomes (see above). A total of four different types of yoga interventions were investigated, including: *Iyengar* or Hatha yoga,[78, 150–152, 208, 209] an integrated yoga program,[77, 154, 221], *Pranayama* or yoga breathing,[122, 220] and Patanjali's Yoga Sutras[124].

A systematic review and meta-analysis assessed the impact of yoga interventions on quality of life and psychological health specifically in breast cancer patients and survivors.[130] Overall, 12 RCTs were included in the analysis with a total of 742 participants. Analyses

revealed short-term effects on improved psychological health, including anxiety ($P < .01$), perceived stress ($P = .03$), and psychological distress ($P < .01$). It is, however, notable that these effects were only applicable to those who engaged in yoga during active cancer treatment and not in the post-treatment period. The authors state that with these positive preliminary results, yoga should be used in this population.

Risk/benefit assessment of yoga interventions: As stated above regarding yoga for anxiety/stress and for depression/mood disturbances, yoga can be adapted and modified for use in this population with low risk to the patient. Overall, yoga has shown preliminary efficacy in improving quality of life, and is recommended for use with breast cancer patients.

Future research in yoga interventions for quality of life/physical functioning: As stated earlier, future trials of yoga to improve quality of life/physical functioning should examine the effects of different types, doses, and durations of yoga on quality of life outcomes. Higher quality trials, including trials with larger and more diverse samples, should be conducted.

C and D graded therapies for quality of life/physical functioning—Trials in acupuncture[130, 132, 203, 235, 236], Qigong[222, 223], reflexology[224–226], and mistletoe[227–230] have assessed the effect of these therapies on quality of life/physical functioning and received a C Grade indicating that they can be considered for use. The five trials evaluating acupuncture had mixed findings and small sample sizes; future studies should replicate the trials of acupuncture that compared real and sham acupuncture, which were the study designs showing no effect.[130, 132, 203, 235, 236] Two trials [222, 223] found qigong to have beneficial effects on quality of life, however, the studies were fairly small and should be replicated in larger and more diverse patient populations. Three large high-quality trials[224–226] of reflexology for improving quality of life reported mixed findings.

There is some evidence that mistletoe may improve the quality of life in breast cancer patients[227–230]. However, while the trials have study quality and sample sizes that could merit a “B” grade, the final decision to assign a “C” grade is due to two areas of uncertainty. First, while several different preparations and formulations have been found to be effective in trials of moderate size, the assessment does not result in a higher grade because of the non-specificity and variability of formulations of agents tested. Secondly, mistletoe is an injected bioactive compound with a potential for a differential risk benefit ratio due to toxicities and drug interaction with standard cancer therapies that may not be detected in smaller studies; a similar stringency need not to be applied to mind-body interventions as they have lower risk profiles. The Grade C recommendation is based on four RCTs, completed between 2004 and 2014, which tested the use of mistletoe for improving quality of life.[227–230] Quality of life was the primary outcome in all four trials where a mistletoe product group was compared with placebo[227, 228] or standard care[229, 230] control group. The mistletoe products tested, all injected subcutaneously, included PS76A2[227, 228], Helixor A[230], and Iscador[229]. Study participants included women receiving chemotherapy treatment for breast cancer and sample sizes ranged from 61 to 352 participants. To improve specificity of the effectiveness of mistletoe as a treatment for improved quality of life in breast cancer patients, double blind trials need to directly evaluate and compare the different

products available and also assess long-term benefit and safety from the use of mistletoe products. Trials of bioactive agents carry the additional requirement of adequate size and statistical power to exclude drug interactions and attenuation of cancer outcome benefits of concurrently administered adjuvant treatments. Two systematic literature reviews[48, 231] of controlled clinical trials of mistletoe, including a Cochrane database analysis, did find an improvement in survival in the adjuvant setting. Though this outcome is outside the scope of this current review, the two reviews found a suggestion of benefit for quality of life and called for further confirmatory trials.[48, 231]

Use of Integrative Therapies for Chemotherapy Induced Nausea and Vomiting (CINV)

Description of chemotherapy-induced nausea and vomiting—Chemotherapy-induced nausea and vomiting (CINV) is experienced by some cancer patients following chemotherapy administration.[232–234] Acute CINV is typically defined as occurring during the first 24-hour period following chemotherapy administration. Delayed or late CINV is felt to be mediated by different mechanisms compared to acute CINV [235] and occurs more than 24 hours following chemotherapy administration. In a large prospective study of breast cancer patients receiving chemotherapy treatments, 37% reported any nausea and 13% reported any vomiting at the first 24-hour period. [236] In the 2–5 days following chemotherapy administration: 70% reported any nausea and 15% reported any vomiting. [67, 236] Consequences of CINV include dehydration, serious metabolic derangements, nutritional depletion and anorexia, deterioration of physical and mental status, withdrawal from potentially useful and curative antineoplastic treatment, and decrease in self-care and functional ability. CINV is considered to be one of the most severe and feared adverse effects of cancer treatment by patients and can have a significant impact on quality of life. [232, 237–239] Standard of care anti-emetics for managing CINV have changed considerably in the last 5 years, thus many of the trials evaluating integrative approaches are not tested with the newest and most effective standard treatment regimen.[233, 234] Most contemporary studies use the endpoint of proportion of patients achieving a complete response defined as no emesis or use of rescue medication. Additionally, anti-emetics themselves have side effects such as headaches, constipation, and neuropsychiatric effects and therefore merit study designs that replace medications with integrative approaches and use equivalence or non-superiority designs for the CINV endpoints and medication side effect endpoints.

Acupressure (B grade)

Overview of acupressure interventions for CINV: For breast cancer patients receiving chemotherapy, acupressure can be considered as an addition to anti-emetics to help control nausea and vomiting (Grade B). This recommendation is based on results from three RCTs, reported between 2000 and 2007, of an acupressure intervention used in conjunction with antiemetics to treat CINV (Supplemental Table 5).[240–242] Acute and delayed nausea and vomiting were the primary outcomes for all three trials. In two trials[240, 242], the acupressure plus usual care intervention group was compared with a usual care group. The third trial[241] was a three-arm trial comparing 1) true acupressure at the P6 and SI3 points in addition to usual care; 2) sham acupressure, or placebo acupressure on a different acupressure point, in addition to usual care; and 3) usual care only. (Of note, the use of sham controls in acupressure and acupuncture studies is to attempt to control for the experience of receiving

the treatment and if implemented well, participants will not be able to discern between the true and sham techniques.) Study participants included breast cancer patients undergoing the first, second, or third cycle of chemotherapy. The study sample sizes in the trials ranged from 17 to 160 participants. The acupressure interventions included self-acupressure[240, 241] using a finger and wearing acupressure wristbands.[242] Across the three trials, acupressure therapy produced significant decreases in nausea, retching, and vomiting ($P < 0.05$ for multiple outcomes assessing CINV; see Supplemental Table 5 for details).

A review assessing acupressure as a nonpharmacologic adjunctive intervention for CINV control across all cancers concluded that acupressure should be strongly recommended as an effective intervention along with standard care for CINV control.[243] Other studies of acupressure to reduce nausea and vomiting have shown efficacy in other populations, including pregnant women and postoperative patients, including after thyroidectomy.[244] All of these studies were conducted with acupressure wristbands placed on both the patient's arms at the PC-6 acupoint.[245] A review of acupuncture and acupressure for CINV control among breast cancer patients concludes that the therapies are both safe and effective.[246] A secondary data analysis of the Dibble et al.[241] multi-center study concluded that breast cancer patients whose nausea intensity started higher from the acute phase continued to experience higher symptom intensity during the 11 days after chemotherapy administration and required more frequent acupressure on acupressure point PC6 even after the peak of nausea.[247] However, a recent publication by Molassiotis, a lead author of one of the included trials in our review,[248] suggests an overall placebo effect in the study of acupressure for control of CINV, although this interpretation included a mix of cancer populations and was not limited to breast cancer patients.

Risk/benefit assessment of acupressure interventions: Self-administered acupressure is easy to perform, safe, cost-effective, noninvasive, does not interfere with a patient's privacy, and has no deleterious effects on patients. Acupressure can be performed anywhere with little or no equipment.

Future research in acupressure interventions for CINV: Future research in this area could assess how to identify the best patients that can be instructed to perform self-administered acupressure, when acupressure can be performed, and whether additional points can be administered along with PC6 to increase the effectiveness of self-administered acupressure to reduce nausea and vomiting.

Electroacupuncture (B grade)

Overview of electroacupuncture interventions for CINV: Electroacupuncture or acustimulation can be considered as an addition to antiemetics to control CINV in breast cancer patients during chemotherapy (Grade B). This recommendation is based on two RCTs, published in 2000 and 2012 (Supplemental Table 5)[249, 250], as well as the 1997 NIH Consensus Conference on acupuncture.[251] However, most of these trials predated the use of newer agents including 5-HT3 or NK1 receptor antagonists, which have become standard anti-emetic therapies for patients receiving highly emetogenic chemotherapy. We do not have a body of evidence to evaluate whether the addition of acupuncture to contemporary

anti-emetics yields added benefit. Participants in the trials in this analysis included breast cancer patients who had received moderately high or highly emetogenic chemotherapy without a 5-HT3 or neurokinin-1 (NK1) receptor antagonist.[234] Both trials used PC-6 and ST-36 acupoints and sham controls, and both trials evaluated the effects of these acupoints on acute and delayed CINV. One trial additionally used acupoint LI-4[249] and found that electroacupuncture was no better than sham electroacupuncture and that a likely contributor to the lack of effect of electroacupuncture in CINV is the fact that the study evaluated only feasibility with minimal electroacupuncture intervention and without a no-acupuncture arm.[249] The second trial[250] found that patients receiving electroacupuncture experienced significantly fewer emesis episodes over the five days of the acupressure intervention than did patients receiving mock therapy or antiemetics alone ($P < 0.001$). Between-group differences in the number of emesis episodes were also significant for electroacupuncture versus minimal needling ($P < .001$) and for minimal needling versus antiemetics alone ($P = 0.01$).[250]

A multicenter study by Yang et al.[252] that compared ST-36 electroacupuncture plus anti-emetics with anti-emetics alone in 246 patients with heterogeneous cancers indicated an additive effect with the use of electroacupuncture ($P < 0.01$) with greater decreases in nausea and vomiting scores ($P < 0.001$) compared to use of anti-emetics alone. Two early studies by Dundee et al.[253, 254] reported significantly less CINV with a PC-6 electroacupuncture intervention, although investigators noted that the brevity of emetic action was a major problem. In a recent review of acupuncture studies including studies that evaluated CINV, investigators concluded that only the electroacupuncture study of Shen et al.[250] had a low risk of bias.[31] In addition, an earlier meta-analysis by Ezzo et al.[255] determined that electroacupuncture, not manual acupuncture, was beneficial for first-day vomiting and that needle insertion as part of manual and electroacupuncture provides greater intensity of stimulation and produces more beneficial effects than surface electrostimulation.

Risk/benefit assessment of electroacupuncture interventions for CINV: With proper administration, electroacupuncture has been shown to be both safe and effective.[256–261] In addition to possibly reducing CINV, PC-6 stimulation has been associated with other positive benefits, including analgesic,[256] sedative,[262] and anxiolytic effects.[263] Further, because CINV is drug-specific rather than disease-specific, these benefits should extend to CINV in other cancer patient populations, as suggested in the study of Yang et al.[252] with participants who had a variety of cancers. Practical issues to consider are that electroacupuncture should not be used in patients with a pacemaker or implantable defibrillators and that special attention is required when treating patients who are pregnant, have seizure disorders, or are disoriented.[31]

Future research in electroacupuncture interventions for CINV: Future trials on the use of electroacupuncture interventions for CINV in breast cancer patients can focus on the testing the use of electroacupuncture with new standard of care treatment regimens, as well as the dissemination and implementation of this technique in the clinical setting. In addition, nausea that is unrelated to chemotherapy is also a common problem in cancer patients and

this modality could be tested in comparison to less potent anti-emetics or to best supportive care when other therapies are ineffective.

C and D graded therapies for CINV—Three trials of ginger[264–266] and two trials of relaxation[144, 177] have examined their effects on CINV as a primary outcome. Though there were a limited number of trials, results suggested enough of an effect to result in Grade C recommendations stating that ginger and relaxation can be considered as an addition to antiemetics for the control of acute CINV. Future directions in research should focus on replicating trials of these modalities for CINV as the primary outcome. Glutamine is not recommended for improving CINV due to a lack of effect from two trials[267, 268] in which CINV was assessed as a secondary outcome (Grade D).

Use of Integrative Therapies for Acute Radiation Dermatitis

Patients respond to radiation therapy uniquely.[269] As radiation is a localized, targeted therapy side effects are most often locoregional within the targeted area; however, damage to normal local tissues and adjacent organs at risk can result in fatigue as the body expends energy in normal tissue repair. The most common side effect in breast cancer patients is acute skin irritation. Late changes to normal tissue can occur years following therapy and can include soft tissue fibrosis, lymphedema, lung, heart and chest wall damage.[269] Not all patients experience one or all of the side effects of radiation, but patients who do experience acute side effects of radiation typically see the effects go away after several weeks following treatment.[269] Acute radiation dermatitis can occur with radiation therapy and may result in reactions ranging from faint erythema to dry, itchy, and peeling skin and ultimately to moist desquamation and ulceration.[270] The CGCTC is the most common scale to measure acute radiation skin toxicity that is used by cooperative groups during cancer clinical trials and grades skin reactions from 0 to 4 with grade 1 being erythema and grade 4 being ulceration. Most breast cancer patients develop mild to moderate acute skin reactions of grade 1–3 during and shortly after a course of radiation therapy. These reactions usually resolve quickly but can cause significant symptoms, especially with higher grade toxicity.[270]

D graded therapies for acute radiation dermatitis—There are no A, B or C graded therapies to report for acute radiation dermatitis post treatment. Aloe vera gel and hyaluronic cream are both not recommended as a standard therapy to prevent or treat acute radiation dermatitis simply due to lack of effect (Grade D). Our review consisted of two quality studies for each product with large sample sizes for both the aloe vera trials[271, 272] (N=208; N=194) and hyaluronic cream trials[273, 274] (N=200; N=74). Each trial assessed the acute skin reaction from radiation therapy as its primary outcome.

Use of Integrative Therapies for Vasomotor Outcomes

Vasomotor symptoms are common in breast cancer patients and include hot flashes, intense sweating, flushing on the face and chest, and may come with heart palpitations and anxiety.[275] These symptoms occur episodically, including nocturnally when night sweats can significantly disrupt women's sleep. According to NCI, about two thirds of postmenopausal women with a history of breast cancer experience hot flashes. These symptoms may occur naturally or as a consequence of surgery, chemotherapy or endocrine therapy.[276] While

vasomotor symptoms may resolve on their own, 20% of affected women suffer from persistent hot flashes four years later after last menses.[275] Together, vasomotor symptoms can significantly impact women's quality of life.[276]

C and D graded therapies for vasomotor outcomes—There are no A or B graded therapies to recommend for vasomotor outcomes. Acupuncture can be considered as a therapy for hot flashes based upon nine trials assessing acupuncture for hot flashes (Grade C).[134, 189, 190, 277–282] Seven trials assessed hot flashes as the primary outcome and only one trial[282] had more than 100 participants. Overall, the literature showed mixed findings; however, the single large trial showed significant reductions in hot flashes in their electroacupuncture group compared to sham and control groups. The use of soy as a therapy for hot flashes is not recommended due to lack of effect (Grade D). Three large trials[283–285] assessed soy for the treatment of hot flashes as the primary outcome and showed a lack of effect.

Use of Integrative Therapies for Lymphedema

Lymphedema—Lymphedema is a condition following treatment such as surgery or radiation therapy where parts of the lymph system become damaged or blocked, leading to an accumulation of lymph fluid that does not drain properly, builds up in tissues, and causes swelling.[35] The CTCAE grades edema of the limbs from grade 1 (5–10% interlimb discrepancy) up to grade 3 (>30% interlimb discrepancy). Lymphedema commonly affects the arm or leg but can also impact other parts of the body. For breast cancer patients and survivors, lymphedema is most common in the upper extremities and sometimes in the breast and/or chest wall, and can occur up to 30 years following treatment. Owing to difference in diagnosis and characteristics of patients studied, and inadequate follow-up the overall incidence of arm lymphedema after breast cancer has been found to range from 8% to 56%.[286] Breast cancer survivors with arm lymphedema in particular have been found to have decreased quality of life and increased psychological distress and disability compared to survivors without lymphedema.[286–288]

C graded therapies for lymphedema—There are no A or B graded therapies to report for lymphedema. Two trials assessed laser therapy[289, 290] and seven trials assessed manual lymphatic drainage[291–297] for the treatment of lymphedema as a primary outcome. The two trials evaluating laser therapy were small in sample size and showed mixed findings. Only two of the seven trials assessing manual lymphatic drainage had a sample size greater than 100 participants[292, 297]. Overall, the literature suggests that manual lymphatic drainage and compression bandaging are equivalent. Thus, either therapy can be considered as treatment options for lymphedema, with manual lymphatic drainage being considered for those who have sensitivity to bandaging (Grade C).

Use of Integrative Therapies for Chemotherapy Induced Peripheral Neuropathy (CIPN)

Chemotherapy induced peripheral neuropathy (CIPN)—Cancer treatments, including chemotherapy, may cause damage to the peripheral nerves resulting in neuropathy.[298] The CGCTC categorizes neuropathy under neurologicsensory and grades from 0–3 with 3 being severe objective sensory loss or paresthesias that interfere with function. Sensory

neuropathy can include symptoms of pain, tingling, numbness, or a pins-and-needles feeling, the inability to feel a hot or cold sensation, or the inability to feel pain. Motor neuropathy can include problems with balance, weak or achy muscles, twitching, cramping or wasting muscles, or swallowing or breathing difficulties. Autonomic nerve damage can cause dizziness or faintness, and digestive, sexual, sweating and urination problems. [298]

H graded therapies for CIPN—There are no A or B graded therapies to report for the prevention or treatment of CIPN. Acetyl-L-carnitine is not recommended as a standard therapy to prevent or treat CIPN due to harm (Grade H). A single large and high-quality study[200] assessing the use of acetyl-L-carnitine capsules to prevent CIPN following taxane therapy as a primary outcome (N=409) found that acetyl-L-carnitine administered during taxane chemotherapy was associated with worse CIPN symptoms.

Use of Integrative Therapies for Pain

Pain—According to the International Association for the Study of Pain, pain can be defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage.”[299] The CTCAE grades pain from 1 (mild) to 3 (severe, limiting self care). Pain can be caused by cancer therapies, including surgery, radiation therapy, chemotherapy, targeted therapy, supportive care therapies and/or diagnostic procedures.[300] Pain is commonly experienced by breast cancer patients with a prevalence ranging from 40–89%. [299] Pain management requires proper assessment including measurement of intensity.[300] It is also important to evaluate the impact of pain on the patients physical, mental, and social health as pain can negatively impact a patient’s functional status and quality of life. Pain management can include both pharmacologic and non-pharmacologic modalities. Proper education about treatment and longitudinal follow-up are essential.

C graded therapies for pain—There are no A or B graded therapies to report for pain. Energy [301] and healing touch[192] for pain following chemotherapy, music therapy[104, 107] and hypnosis[302, 303] for pain following surgery, and acupuncture[304–308] for pain associated with aromatase inhibitor associated musculoskeletal symptoms were examined and each received a C grade indicating that they can be recommended as a therapy for pain. A single large trial assessed healing touch[192] for pain following chemotherapy as a secondary outcome showing small positive effects favoring the therapy. Similarly, two trials assessed music therapy[104, 107] and hypnosis[302, 303] for pain following surgery as a primary outcome showing small positive effects favoring the therapy. However, there is a lack of multiple large trials to support each therapy. Finally, five trials evaluated acupuncture for pain associated with aromatase inhibitor-associated musculoskeletal symptoms as the primary outcome.[304–308] All trials had small sample sizes and reported mixed findings.

Use of Integrative Therapies for Sleep Disturbance

Sleep disturbances—Studies have shown that nearly half of all breast cancer patients have sleep-related problems due to a range of causes including side effects of antineoplastic medications, long hospital stays, or stress.[309, 310] In addition, a growing number of breast cancer patients are obese,[311] which increases the incidence of sleep apnea, a major cause for insomnia. Insomnia, a specific sleep disorder of initiating and maintaining sleep, is most

common in cancer patients and often occurs along with anxiety and depression.[312] The CTCAE measures insomnia under psychiatric disorders from grade 1–3, with grade 3 being severe difficulty falling asleep, staying asleep or waking up early.

C graded therapies for sleep disturbance—There are no A or B graded therapies to report for sleep disturbance. Yoga can be considered for sleep disturbance (Grade C). Five trials assessed yoga for sleep disturbance[73, 121, 124, 152, 313] and in four of these trials sleep was a secondary outcome. Two trials were of high quality with more than 100 participants[73, 313]. Overall, the body of literature showed no greater effect in sleep quality than health education classes, stretching groups, and wait list control.

CONCLUSION

In this review, we closely examined and described the RCTs that provide support for the highest graded therapy recommendations for the use of integrative therapies during the patient experience of breast cancer and for side effects related to breast cancer treatment. High levels of evidence support the routine use of mind-body practices, such as yoga, meditation, relaxation techniques and passive music therapy to address common mental health concerns among breast cancer patients, including anxiety, stress, depression, and mood disturbances. Additionally, meditation has been shown to improve quality of life and physical functioning, and yoga has been found to improve quality of life and fatigue. Massage has been shown to improve mood and acupressure and electroacupuncture decrease CINV. Given the high level of evidence of benefit coupled with the and the relative low level of risk, these therapies can be incorporated as an option care for patients, especially when there is poor symptom control. As is the case with many standard therapies, the impact of integrative approaches on symptom management is highly individualized. Therefore, a patient-centered trial and evaluation approach may be needed and can be guided by the grade of recommendations and altered as needed along with the incorporation of patient preferences. In addition to the modalities discussed in this review that were given lower grade (C or D), patients are using many other forms of integrative therapies with little or no supporting evidence; this serves as a compelling call for further research to support patients and health care providers in making more informed decisions that avoid harm. In the meantime, while further clinical evaluation is underway, clinicians and patients need to be cautious about the use of therapies that received a Grade of C or D and need to fully understand the potential risks and benefits of use, including the risk associated with not using a conventional therapy that may effectively prevent or treat the condition. For example, in a patient with incurable disease who has marked symptoms not adequately managed with conventional therapies, carefully monitored use of a Grade C therapy could be medically reasonable even though more research clearly would be needed to apply this broadly across a patient population. This review and others support referral or provision of clinical services to include both evidence-based conventional and integrative therapy options.

The limited number of integrative modalities with A or B grades emphasizes the need for all cancer care providers to initiate a dialogue early in their relationship with cancer patients to develop a framework for how evidence forms the basis for all clinical decisions. Patients and

clinicians should engage in shared decision making based on the best available evidence on the benefits and harms, while reflecting patient values and preferences. A careful appraisal of the evidence base for integrative therapies can help allay a patient's concern that their care team is informed and not overlooking options that may be of interest to them. In addition, such an appraisal of the evidence will offer those modalities that do merit consideration and allow for better personalization of care and shared decision making.

This systematic review with grades of evidence adds to a growing literature base including reviews of integrative therapy for breast cancer and other cancer populations. For example, there are numerous reviews that support the use of integrative therapies including passive music therapy[109], stress management programs[116], various yoga practices[129], meditation and MBSR[96], massage[170], and relaxation techniques[180] as adjunctive therapies for psychological outcomes, specifically the anxiety/stress and depression/mood outcomes assessed in this review. Acupressure for CINV is also well supported in the review literature across all cancer patients.[243] There are mixed findings in the areas of meditation and MBSR for quality of life, [45, 98], and electroacupuncture for CINV,[31] which suggests overall low quality or too few studies. Thus, future research on the impact of these integrative therapies on the relevant clinical outcomes is warranted. A limitation to the generalizability of our findings is that the majority of participating subjects in the clinical trials evaluated were non-Hispanic white women with high socioeconomic status relative to the general population. In addition, none of the trials examined age-related responses, and or differential responses in pre- vs. post-menopaual women. There is a clear need to design well-powered controlled trials using the best standard treatment control or an appropriate placebo.

Challenges of implementing integrative therapies in breast oncology

Cancer patients face a number of psychological and physical challenges as they move through cancer diagnosis, treatment and survivorship. According to NCCN guidelines, comprehensive clinical programs should systematically screen for cancer-related symptoms and side effects in the process of mandated screening for distress. This review and others support subsequent referral or provision of clinical services to include both evidence-based conventional and integrative therapy options.[66, 314]

Based on recent estimates from the U.S. National Health Interview Survey, 75% of individuals with a history of cancer use one or more complementary and integrative therapies.[315] Many North American cancer centers now operate formal integrative oncology programs. As most of these services are not reimbursable by insurance, the methods and models of funding and implementing these programs vary; some programs and services are fully funded and provided free of charge to patients, some are entirely paid for out-of-pocket by patients, and some are a combination of the two. Often mind-body therapies are available from trained clinical staff already employed at cancer centers, such as oncology nurses or social workers, and hence, are more readily accessible at low or no cost. Others such as massage therapy and acupuncture may be covered by some forms of insurance, varying by country, province/territory and state.

Implementing complementary and integrative therapies in a clinical setting not only requires funding and infrastructure, but also requires well-trained, knowledgeable providers. Many of

the integrative therapies do not have a one-size-fits-all approach and need to be provided and administered by appropriately trained practitioners who can evaluate which are the best forms and techniques to use with a specific patient. Though training and credentialing for many integrative providers varies by jurisdictions, best practices suggest that providers be trained to the highest standard of their profession, even if that exceeds the state or province-based standards, such as a requirement for institutional credentialing that may include proctoring. As the fields of integrative therapies are expanding, there are now new professional associations that specialize in oncology, for example the Society for Oncology Massage and the Oncology Association of Naturopathic Physicians.[316, 317]

Future research

Rigorous clinical research that appropriately reflects integrative care as it is used in the community and at integrative cancer centers is needed to responsibly move this field forward. Integrative modalities can be tested in addition to standard supportive treatments, or even in place of them, if the standard therapy is associated with side effects or significant costs and the trial design allows for early discontinuation in the event of futility. Clinical trials designed to test efficacy in tightly controlled academic research settings are often testing protocols that are not realistically implementable in the community setting. Implementation and dissemination research designs to consider include pragmatic trials that involve multi-modal therapies that are applied in the manner in which they are typically offered in clinical settings. This approach, while unable to pinpoint clear causal relationships between specific interventions and outcomes, allows an exploration and evaluation of clinical impact that is more truly generalizable. Head-to-head comparisons of different integrative therapies and conventional symptom management therapies would help provide some specificity and direction for health care providers making recommendations to patients. Comparative effectiveness research testing integrative modalities in relationship to pharmacological and other approaches would also be informative in providing options as well as comparisons of toxicities and cost effectiveness. Studies that examine mechanism of action are also needed, however, the emphasis here is on trials of agents that are actively in use, unlike novel pharmacological therapies. Importantly, interventions need to be tested in economically and culturally diverse patient populations in order to understand the applicability of an intervention to the growing population of cancer survivors.

Future studies need to include systematic assessments of treatment toxicities, including toxicities from both the integrative and the convetional therapies. In this review, when possible, the NCI Common Terminology Criteria for Adverse Events (CTCAE) are used to describe cancer treatment side effects. However, many of the trials did not report toxicities or adverse events, and among the trials that did, the majority of the trials did not assess toxicities and adverse events systematically. The CTCAE are a set of criteria for the standard grading and classifications of adverse effects of drugs used in cancer therapy and the FDA is increasingly using CTCAE patient reported outcomes (CTCAE-PROs) to monitor treatment side effects.[318, 319] Ideally, trials will include systematic evaluation of both provider (i.e., CTCAE) and patient (i.e., CTCAE-PROs) assessments of adverse events. If future trials do not use these methods, at minimum, validated measurement tools need to be used to allow for ongoing quantitative assessments of adverse events using robust statistical analyses.

Ongoing challenges include the inability to blind subjects to most of the integrative modalities studied, as most measures are subjective and thus susceptible to suggestive biases in which patients perceive benefit to an intervention simply because they are receiving it. Using a mixed methods model of research including both qualitative inquiry that explores the patient's experience of their treatments and quantitative data will be helpful to validate and better justify the use of integrative therapies. Additionally, the use of both subjective and objective patient-reported outcomes should be employed within a mixed methods model. This approach can be used in both clinical trials or in prospective observational studies. To better enable real clinical uptake and change, knowledge translation experts, cancer patients, policy makers and decision makers should be involved in both study design and interpretation to better enable integration of these therapies into clinical practice.

In conclusion, awareness of the base of evidence for complementary and integrative therapies based on the recently published SIO guidelines and the emerging literature should be a core competence for the cancer care provider and should be applied in decision making with breast cancer patients requiring supportive care. Billions of dollars are spent each year on complementary and integrative health therapies, with unknown benefits and for those that have thus far been shown to be ineffective.[320] Research in this area could save large amounts of healthcare dollars and resources and more importantly can redirect patients to treatments with known benefits and better safety profiles. This article provides greater depth of discussion of these interventions, such that clinicians and patients can begin the process of integration, based upon patient needs in their specific setting and context.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Graded integrative therapies for use in breast cancer patients according to clinical outcomes*

Clinical Outcomes	Recommended therapy	Strength of Evidence Grade
Acute Radiation Skin Reaction	Aloe vera[271, 272] and Hyaluronic acid cream[273, 274] should not be recommended for improving acute radiation skin reaction.	D
Anxiety/Stress Reduction	Meditation is recommended for reducing anxiety.[69–72, 89]	A
	Music therapy is recommended for reducing anxiety.[104–108]	B
	Stress management is recommended for reducing anxiety during treatment, but longer group programs are likely better than self-administered home programs or shorter programs.[112–115]	B
	Yoga is recommended for reducing anxiety.[75, 117–124]	B
	Acupuncture[134–136], Massage[137–140], Relaxation[141–145] can be considered for reducing anxiety.	C
Chemotherapy Induced Nausea and Vomiting	Acupressure can be considered as an addition to anti-emetics drugs to control nausea and vomiting during CT. [321–323]	B
	Acupuncture can be considered as an addition to anti-emetics drugs to control vomiting during CT.[324, 325]	B
	Ginger[265, 266, 326], Relaxation[144, 177] can be considered as an addition to anti-emetics drugs to control nausea and vomiting during CT.	C
	Glutamine[267, 268] should not be recommended for improving nausea and vomiting during CT.	D
Depression/Mood Disturbance	Meditation, particularly MBSR, is recommended for treating mood disturbance and depressive symptoms. [69–72, 89, 159–163]	A
	Relaxation is recommended for improving mood disturbance and depressive symptoms.[141, 144, 145, 177–179]	A
	Yoga is recommended for improving mood and depressive symptoms.[73–76, 117–119, 121–124, 150–152]	B
	Massage is recommended for improving mood disturbance.[138–140, 167–169]	B
	Music therapy is recommended for improving mood.[106, 108, 146, 147]	B
	Acupuncture[134–136, 189, 190], Healing Touch[191, 192], Stress Management[112–114, 193, 194] can be considered for improving mood disturbance and depressive symptoms.	C
Fatigue	Hypnosis[79, 80] and ginseng[203] can be considered for improving fatigue during treatment.	C
	Acupuncture[136, 205–207] and Yoga[73, 74, 78, 121, 152, 209, 327] can be considered for improving fatigue post treatment.	C
	Acetyl-L-carnitine[200] and Guarana[201, 202] should not be recommended for improving fatigue during treatment.	D
Lymphedema	Laser therapy[289, 290], Manual lymphatic drainage and compression bandaging[291–297] can be considered for improving lymphedema.	C
Neuropathy	Acetyl-L-carnitine is not recommended for prevention of neuropathy in breast cancer patients due to harm.[200]	H
Pain	Acupuncture[256, 304–308], Healing Touch[192], Hypnosis[302, 303], Music therapy[104] can be considered for the management of pain.	C
Quality of life	Meditation is recommended for improving quality of life.[69–71, 160–162, 216]	A

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Clinical Outcomes	Recommended therapy	Strength of Evidence Grade
	Yoga is recommended for improving quality of life.[77, 78, 119, 122, 124, 150–153, 208, 209, 220]	B
	Acupuncture[134, 136, 206, 328, 329], mistletoe[229, 230, 321, 322], Qigong[222, 223], Reflexology[224–226], Stress management[59, 112–114, 193, 194, 330] can be considered for improving quality of life.	C
Sleep disturbance	Gentle yoga[73, 121, 124, 152, 313] can be considered for improving sleep.	C
Vasomotor/Hot flashes	Acupuncture[134, 189, 190, 277–282] can be considered for improving hot flashes.	C
	Soy[283–285] is not recommended for hot flashes in BC patients due to lack of effect.	D

Abbreviations: BC, Breast Cancer; CT, Chemotherapy; MBSR, Mindfulness-Based Stress Reduction

Notes: The clinical population is breast cancer (BC) patients during treatment, including surgery, chemotherapy, hormonal/biological therapy, and radiation therapy. The clinical question is “What integrative therapies can be used to prevent, treat and manage symptoms and side effects encountered during breast cancer treatment?” Definitions of the Grade of Recommendations are listed below.[10]

Grade A: Recommends the modality. There is high certainty that the net benefit is substantial. Offer/provide this modality.

Grade B: Recommends the modality. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. Offer/provide this modality.

Grade C: Recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small. Offer/provide this modality for selected patients depending on individual circumstances.

Grade D: Recommends against the service. There is moderate or high certainty that the modality has no net benefit. Discourage the use of this modality.

Grade H: Recommends against the service. There is moderate or high certainty that the harms outweigh the benefits. Discourage the use of this modality.

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Table 2

Training and licensure information for A and B grade integrative therapies

Modality or Therapy	Training	Licensure and Regulation	Professional Societies and Organizations
Acupuncture, electro-acupuncture, and acupressure	Licensed acupuncturists generally have attended formal schools of Asian medicine and have passed national certification examinations in order to sit for state or provincial licensing exams. The Accreditation Commission for Acupuncture and Oriental Medicine (ACAOM) accredits schools of Asian medicine in the U.S. Degrees include the Masters of Acupuncture requiring a minimum of 3 years and 1900 hours of training and the Masters of Acupuncture and Oriental Medicine requiring a 3–4 year program, averaging 2,700–3,465 hours of training. Advanced degrees include Doctor of Acupuncture and Oriental Medicine (DAOM), Oriental Medicine Doctor (OMD), Doctor of Acupuncture and Chinese Medicine (DACM) and Doctor of Oriental Medicine (DOM) who provide advanced evaluations, integrative medicine as well as acupuncture and herbal therapy and can provide access to the whole breadth of Chinese medicine. Advanced degrees require a Masters level degree with additional 1000+ hours of training. The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) offers acupuncture, herbal and Oriental medicine certifications on a national level.[24]	US: Acupuncture and Chinese herbology and Oriental medicine are regulated via state licensing bodies. NCCAOM reports 44 states plus the District of Columbia have acupuncture practice acts. 43 states currently require passage of NCCAOM national examinations for initial licensure. The NCCAOM certifies acupuncture, Chinese herbology and Oriental medicine. Currently, California requires passage of its own state examinations for licensure and does not accept the NCCAOM. A subset of states regulate acupressure under acupuncture or massage regulations. CANADA: Acupuncture is regulated via provincial licensing bodies in the provinces of British Columbia, Alberta Ontario, Quebec and Newfoundland. Chinese medicine is currently only regulated in British Columbia and Ontario.	The Accreditation Commission for Acupuncture and Oriental Medicine (ACAOM): http://www.acaom.org National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM): http://mx.nccaom.org College of Traditional Chinese Medicine Practitioners and Acupuncturists of British Columbia (CTCMA): http://www.ctcma.bc.ca College of Traditional Chinese Medicine Practitioners and Acupuncturists of Ontario (CTCMPAO): http://www.ctcmpao.on.ca/ College and Association of Acupuncturists of Alberta (CAAA:): http://acupuncturealberta.ca/ Association of Acupuncturists of Quebec (AAQ):http://www.acupuncture-quebec.com/en/home.html Newfoundland and Labrador Council of Health Professionals (nlchp): http://www.nlchp.ca/
Hypnosis	Mental health and medical professionals typically practice hypnosis as a specialty or sub-specialty. Certified hypnotherapists, in general, hold a graduate-level or bachelor's-level degree in a broad range of specialties including: MD, registered nurse, dentist, social worker, licensed counselor or psychologist. pastoral counselor, ordained minister, chiropractor, among many others, prior to obtaining training in hypnosis. At present, there are no accredited schools offering standard college or university degrees in hypnosis; therefore, training in one of the above professions is typically required prior to acceptance into one of many training or certification programs. These programs have a wide range of training requirements, but in general require anywhere from 50 to 200 hours of classroom and clinical training prior to certification.	US: To be certified as a clinical hypnotherapist, applicants typically require anywhere from 50 to 200 hours or training, and often years of experience. There are a number of certification programs with a range of requirements (see links). Regulations for the practice of hypnosis vary on a state-by-state basis (http://www.aihcp.org/hypnosis-regulation.htm). Typically clinical hypnotherapists must renew their certification every 2 to 4 years and have completed 20+ hours of approved training during that time. CANADA: Certification is similar to the US however requirements are much higher, between 225 and 1100 hours: https://www.archcanada.ca/ The Council of Professional Hypnosis encompasses many professional societies and organizations listed: http://www.copho.com/org.htm.	Association of Registered Clinical Hypnotherapists (ARCH): https://www.archcanada.ca/ American College of Hypnotherapy at the American Institute of Health Care Professionals: http://aihcp.net/american-college-of-hypnotherapy/ American Society of Clinical Hypnosis (ASCH): http://www.asch.net/ Hypnosis Motivation Institute (HMI): https://hypnosis.edu/ National Board for Certified Clinical Hypnotherapists (NBCCH): http://www.natboard.com The International Society of Hypnosis (ISH): http://www.ishhypnosis.org/ Society for Clinical and Experimental Hypnosis (SCEH): http://www.sceh.us/ The Milton H. Erickson Foundation: http://www.erickson-foundation.org/
Massage	Associated Bodywork and Massage Professional (ABMP) members at the certified or professional levels must possess a valid massage license from a regulated state/province/territory, have completed 500 approved educational hours, or be certified through the National Certification Board for Therapeutic Massage and Body work (NCTMB). Licensed nurse and physical therapists may qualify for membership at either the certified or professional level with a minimum of 50 hours of additional massage therapy training. Board Certification is the highest voluntary credential attainable to massage	US: Massage therapy is regulated by some U.S. states. See link for state-by-state massage licensure information. http://www.massagetherapy.com/careers/stateboards.php CANADA: Massage therapists can only be registered not licensed in Canada. Currently only four provinces regulate massage therapists: Ontario, British Columbia, New Brunswick and	American Massage Therapy Association: http://www.amtamassage.org Associated Bodywork and Massage Professionals (ABMP): www.abmp.com The National Certification Board for Therapeutic Massage and Bodywork (NCTMB): http://www.ncbtmb.org/ Society for Oncology Massage: http://www.s4om.org/

Modality or Therapy	Training	Licensure and Regulation	Professional Societies and Organizations
	therapists and bodyworkers in the profession today. For the requirements of Board Certification, see: http://www.ncbtmb.org/board-certification.	Newfoundland. The website for the Ontario Massage Therapists has links to the four provinces registration procedures and links to other provincial massage organizations.	Massage Therapists' Association of Ontario: https://secure.rmtao.com/massage_therapy/regulation_of_mt/massage_therapy_in_canada.htm
Meditation	Mindfulness-Based Stress Reduction: The Centre for Mindfulness in Massachusetts provides meditation specialist training –: http://www.umassmed.edu/cfm/training/detailed-training-information/teacher-certification-review/ University of California San Diego (UCSD) Center for Mindfulness provides extensive training: http://mbpti.org/ University of Bangor in Wales awards a Masters in Mindfulness and also has a range of teacher training programs: http://www.bangor.ac.uk/mindfulness/courses.php.en Centre for Mindfulness Studies in Toronto, Canada offer one-day workshops as well as intensive professional training in Mindfulness-Based Cognitive Therapy (MBCT). http://www.mindfulnessstudies.com/	In both the US and Canada board certification is the highest credential attainable for meditation teachers in the healthcare profession today. There is no registration or licensure currently available. Completing mindfulness teacher training courses at one of the recognized training programs, in addition to professional certification, would be the optimal level of training for providing these interventions.	American Mindfulness Research Association: https://goamra.org/
Music therapy	A professional music therapist holds a bachelor's degree or higher in music therapy from one of over 70 American Music Therapy Association (AMTA) approved college and university programs. Music therapists who currently hold professional designation are listed on the National Music Therapy Registry (NMTR) and are qualified to practice music therapy	Music therapist is regulated by some U.S. states (e.g., North Dakota, Nevada). See link for state-by-state massage licensure information: http://www.cbmt.org/examination/state-licensure/ Currently no Canadian provinces/territories license or regulate music therapists.	The Certification Board for Music Therapists (CBMT): http://www.cbmt.org/ Canadian Association for Music Therapy (CAMT): http://www.musictherapy.ca/en/
Relaxation and Stress Management	Relaxation and stress management are usually provided by trained mental health professionals such as Registered/Chartered/Counseling Psychologists, Psychiatrists, Marital and Family Counselors or, Clinical Social Workers and Nurses. Any of these professions could have specific training in these two modalities.	Typically the aforementioned professionals would take courses in relaxation training or stress management as part of their training.	Every jurisdiction has a college of psychologists and social workers. American Psychological Association (APA): http://www.apa.org/ Canadian Psychological Association (CPA): http://www.cpa.ca
Yoga	There are very stringent criteria to be a yoga instructor and most jurisdictions have their own requirements. Most jurisdictions have criteria in place in order to become a "certified yoga instructor". There are also requirements for specific genres of yoga such as Bikram, Iyengar, Ashtanga, restorative yoga, etc. Most states and provinces/territories have a designation as a certified yoga instructor. In the U.S. and Canada, the Yoga Alliance is the biggest body that registers teachers: https://www.yogaalliance.org/Credentialing/Credentials_for_Teachers; and https://www.yogaalliance.org/Credentialing/CredentialsforSchools; http://www.canadianyogicalliance.com	There are currently no states or Canadian provinces/territories that regulate or license yoga.	Most states and provinces have a professional association (or more than one) for certified yoga instructors.

Table 3

Clincial outcomes and integrative therapies with insufficient evidence to form a clinical recommendation (I-statement)

Outcome	Integrative Therapies
Adherence	Acupressure[331], Multi-Modal [332]
Anemia	LCS101 Combination botanical[333], RG-CMH Combination botanical[334], Shenqi Fuzheng Injection [335]
Anxiety/Stress Reduction	Art Therapy[110, 336], Comprehensive Coping Strategy[337], Electrical Nerve Stimulation[338], Healing Touch[191, 339], Hypnosis[340], Myofascial Release[341], Multi-Modal[342, 343], Reflexology[225, 226, 344], Reiki[345], Tai-Chi[346]
Cardiomyopathy	N-Acetylcystelne[347]
Chemotherapy Induced Nausea and Vomiting	Acupressure[348], Aromatherapy[349], *Agaricus sylvaticus*[350], Cocculine (complex homeopathic Rx)[351], Comprehensive Coping Strategy[337], Massage[137], Nevasic Audio Program[352], Yoga[119]
Cognition	Natural Environment[353], *Ginkgo biloba*[203], Meditation[159], Yoga[354]
Constipation	Self-Management Program[355]
Depression/Mood	Art Therapy[110], Biofield Healing[356], Comprehensive Coping Strategy[337], CoQ10[357], Electrical Nerve Stimulation[338], *Gandoderma lucidium*[358], Guarana[201], Hypnosis[359], Multi-Modal[332, 342, 360, 361], Myofascial Release[341], Qi-gong[222], Reflexology[225, 226], Tai-Chi[346]
Fatigue	Acupressure[331], Acupuncture[135, 362, 363], Biofield Healing[356], Comprehensive Coping Strategy[337], CoQ10[357], *Gandoderma lucidium*[358], Light treatment[364], Massage[168], Meditation[159, 163], Mind-Body Cognitive Therapy[365], Movement[366], Multi-Modal[361, 367, 368], Multivitamin[369], Polarity Therapy[370, 371], Stress Management[372], Qigong[222], Reflexology[226], Relaxation[373, 374], Stress Management[112], Yoga[73, 75, 122, 124, 151, 375]
Lymphedema	CYCLO 3 FORT[376], Electro-therapy[377], Ginkgo forte[378], Pentoxifylline[27, 379], Yoga[380]
Neuropathy	Omega 3 Fatty Acids[381], Vitamin E[382, 383], Acupuncture[329]
Neutropenia/Leukopenia	Cat's Claw[384], LCS101 Combination botanical[333], RG-CMH Combination botanical[334], Mistletoe[230, 385], Shenqi Fuzheng Injection[335]
Pain	Comprehensive Coping Strategy[337, 386], Stress Management[112], Vitamin D2[387], Electrical Nerve Stimulation[338], Cognitive and Behavioral Therapy, Hypnosis[388], Massage[169], Myofascial Release[341], Reflexology[226, 344]
Quality of life	Acupressure[348], Biofield Healing[356], Calendula cream[389], Cannabis[390], Chlorella extract[391], CoQ10[357], Curcuminoids[392], Electrical Nerve Stimulation[338], Electro-therapy[377], Flaxseed[375], *Ganoderma lucidum*[358], Gingko forte[378], Guided Imagery[393], Healing Touch[191], Homeopathy[394–396], Hypnosis[79], Laser therapy[290], Manual Lymphatic Draining[292], Massage[168], Meditation[68, 159], Movement[366, 397], Music Therapy[146], Multi-moda[332, 342, 361, 367, 368, 398 l], Multivitamin[369], Polarity therapy[370, 371], Relaxation[177, 178], Shengi Fuzheng[335], Shark cartilage[399], Soy[283], Supportive-Expressive Group therapy[400], Tai-Chi[346, 401–403]
Physical Functioning	Mind-Body Cognitive Therapy[365], Music Therapy[106], Multi-modal[332], Myofascial Release[341], Reflexology[226], Stress management[113], Tai-Chi[401, 403], Yoga[73, 121, 152, 404]
Radiation therapy induced toxicity outcomes	Adlay Bran Extract[405], Alpha Ointment with Henna[406], Aquaphor-Biafine-RadiaCare[407], Boswella cream[355], Calendula Cream[389, 408], Chamomile[409], Curcumin[410], Glutamine[411], Homeopathic Pills[412], Honey[413, 414], Hydration[415], Massage[416], Oil-In-Water Emulsion[417], Ray Gel[418], What Grass Extract[419], Pentoxifylline & Vitamin E[420, 421]
Sleep disturbance	Acupuncture[134, 135, 328], Calendula cream[389], Meditation[159, 219, 422, 423], Qigong[222], Stress management techniques[112]
Vasomotor Outcomes	Black Cohosh[424, 425], Flaxseed[375], Homeopathy[395, 396], Hypnosis[426], Magnetic therapy[427], Meditation[160], Peppermint[428], Vitamin E[429], Yoga[78, 430]

Notes: Definition of the I Statement: Concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined. Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.