

Clinical Practice Guidelines on the Evidence-Based Use of Integrative Therapies During and After Breast Cancer Treatment

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Additional supporting information may be found in the online version of this article.

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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 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. *CA Cancer J Clin* 2017;67:194-232. © 2017 American Cancer Society.

Keywords: acupressure, acupuncture, breast cancer, complementary therapies, integrative medicine, integrative oncology, massage, meditation, music therapy, stress management, yoga

Practical Implications for Continuing Education

- > To make informed decisions on the use of integrative therapies in the oncology setting, clinicians and patients should understand the level of evidence of associated benefits and harms for each therapy.
- > Based on a systematic review of the literature, the Society for Integrative Oncology makes the following recommendations:
 - Use of music therapy, meditation, stress management and yoga for anxiety/stress reduction.
 - Use of meditation, relaxation, yoga, massage and music therapy for depression/mood disorders.
 - Use of meditation and yoga to improve quality of life.
 - Use of acupressure and acupuncture for reducing CINV.
 - There is a lack of strong evidence supporting the use of ingested dietary supplements or botanical agents as supportive care and/or to manage breast cancer treatment-related side effects.
- > Implementing integrative therapies in a clinical setting requires a coordinated team approach with well-trained providers. Training and credentialing for many integrative providers varies by jurisdictions. Best practices suggest that providers be trained to the highest standard of their profession and educated in other relevant disciplines.

Introduction

Patients with breast cancer and breast cancer survivors are frequent users of complementary and integrative therapies, and there are growing numbers of formal, integrative oncology programs within cancer centers.¹⁻⁶ Various terms are used to describe such therapies, 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 use 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 The SIO adapted methods established by the US Preventive Services Task Force¹⁰ to develop graded recommendations on the use of specific integrative therapies for defined clinical indications based on the 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 (eg, anxiety/stress, fatigue). This review provides an updated set of clinical practice guidelines based on a current, systematic literature review of randomized controlled trials (RCTs) published through December 2015 along with 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 suggests that it should be used as the standard of care and is favorable or equal compared with 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

conclude 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 evaluating the use of integrative therapies in the oncology setting, there is a body of well conducted trials of specific therapies for specific conditions that provides sufficient evidence to warrant recommendations on the therapies as viable options for treating specific conditions.

In this review, we provide 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 or survival endpoints, because very few adequately powered RCTs have examined the effect of integrative therapies on these outcomes. We also provide a definition for each integrative therapy that had a sufficiently large body of evidence to formulate a specific recommendation. 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 the 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, which were based on a systematic review of the literature from January 1, 1990 through December 31, 2013,⁹ we conducted a systematic review of published RCTs 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 RCT; 2) available in English; 3) included $\geq 50\%$ patients with breast cancer and/or reported results separately for patients with breast cancer; 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 patients with breast cancer and breast cancer survivors (see Supporting Information 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 (eg, diet^{12,13} and physical activity¹²⁻¹⁴ 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 (eg, cognitive-behavioral therapy,¹⁵ psychoeducation,¹⁶ counseling,¹⁷ and support groups¹⁶). Other interventions that were excluded were in early or pilot stages of research (eg, attention-restoration therapy) or were not considered to be an integrative oncology therapy for the purposes of the SIO guidelines (eg, prayer, spirituality). Each article was scored according to the 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 US Preventive Services Task Force grading system.¹⁰ Grades were based on 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.

According to 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 the difference between statistical and

clinical significance. The graded recommendations reflect our assessment of the clinical significance based on 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, which made it difficult to describe detailed data on effect sizes across all trials. Although 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. Because of space limitations, *P* values are reported and citations are provided to reference the primary reports for additional details.

Definitions of Complementary and Integrative Therapies

Below are definitions listed alphabetically for each of the complementary and integrative therapies that received a grade of A, B, C, D, or H in the updated clinical practice guidelines.^{20,21} Table 1 displays the graded recommendations.^{10,22-151} Table 2 provides background information on the specific training, licensure, and professional organizations associated with each therapy.¹⁵² 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 patients with cancer and by survivors but do not indicate the level of evidence supporting such use. The guideline recommendations provide a 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 (naturalmedicines.therapeuticresearch.com), Memorial Sloan Kettering Cancer Center's *About Herbs* website (mskcc.org/cancer-care/treatments/symptom-management/integrative-medicine/herbs), and the National Cancer Institute (NCI) Office of Cancer Complementary and Alternative Medicine Therapies: A-Z website (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.¹⁵³ It has demonstrated effectiveness in preventing and treating diabetic neuropathy and thus was of interest to examine in the context of chemotherapy-induced peripheral neuropathy (CIPN). It is a substance made in muscle and liver tissue and is found in foods, including meats, poultry, fish, and some dairy products.

TABLE 1. Graded Integrative Therapies for Use in Patients With Breast Cancer According to Clinical Outcomes^a

CLINICAL OUTCOMES	RECOMMENDED THERAPY	STRENGTH OF EVIDENCE GRADE ^b
Acute radiation skin reaction	Aloe vera ^{22,23} and hyaluronic acid cream ^{24,25} should not be recommended for improving acute radiation skin reaction.	D
Anxiety/stress reduction	Meditation is recommended for reducing anxiety. ²⁶⁻³⁰	A
	Music therapy is recommended for reducing anxiety. ³¹⁻³⁵	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. ³⁶⁻³⁹	B
	Yoga is recommended for reducing anxiety. ⁴⁰⁻⁴⁸	B
	Acupuncture, ⁴⁹⁻⁵¹ massage, ⁵²⁻⁵⁵ and relaxation ⁵⁶⁻⁶⁰ can be considered for reducing anxiety.	C
Chemotherapy-induced nausea and vomiting	Acupressure can be considered as an addition to antiemetics drugs to control nausea and vomiting during chemotherapy. ⁶¹⁻⁶³	B
	Electroacupuncture can be considered as an addition to antiemetics drugs to control vomiting during chemotherapy. ^{64,65}	B
	Ginger ⁶⁶⁻⁶⁸ and relaxation ^{59,69} can be considered as additions to antiemetic drugs to control nausea and vomiting during chemotherapy.	C
	Glutamine ^{70,71} should not be recommended for improving nausea and vomiting during chemotherapy.	D
Depression/mood disturbance	Meditation, particularly MBSR, is recommended for treating mood disturbance and depressive symptoms. ^{26-30,72-76}	A
	Relaxation is recommended for improving mood disturbance and depressive symptoms. ^{56,59,60,69,77,78}	A
	Yoga is recommended for improving mood and depressive symptoms. ^{40-43,45-48,79-85}	B
	Massage is recommended for improving mood disturbance. ^{53-55,86-88}	B
	Music therapy is recommended for improving mood. ^{33,35,89,90}	B
	Acupuncture, ^{49-51,91,92} healing touch, ^{93,94} and stress management ^{36-38,95,96} can be considered for improving mood disturbance and depressive symptoms.	C
Fatigue	Hypnosis ^{97,98} and ginseng ^{99,100} can be considered for improving fatigue during treatment.	C
	Acupuncture ^{51,101-103} and yoga ^{45,80,84,104-106} can be considered for improving post-treatment fatigue.	C
	Acetyl-L-carnitine ¹⁰⁷ and guarana ^{108,109} should not be recommended for improving fatigue during treatment.	D
Lymphedema	Low-level laser therapy, ^{110,111} manual lymphatic drainage, ¹¹²⁻¹¹⁸ and compression bandaging ¹¹⁴⁻¹¹⁶ can be considered for improving lymphedema.	C
Neuropathy	Acetyl-L-carnitine is not recommended for the prevention of chemotherapy-induced peripheral neuropathy in patients with BC due to potential harm. ¹⁰⁷	H
Pain	Acupuncture, ¹¹⁹⁻¹²⁴ healing touch, ⁹³ hypnosis, ^{125,126} and music therapy ^{31,34} can be considered for the management of pain.	C
Quality of life	Meditation is recommended for improving quality of life. ^{27-29,73-75,127}	A
	Yoga is recommended for improving quality of life. ^{43,46-48,82-85,104-106,128}	B
	Acupuncture, ^{49,51,102,129,130} mistletoe, ¹³¹⁻¹³⁴ qigong, ^{135,136} reflexology, ¹³⁷⁻¹³⁹ and stress management ^{36-38,95,96,140,141} can be considered for improving quality of life.	C
Sleep disturbance	Gentle yoga ^{45,48,79,84,142} can be considered for improving sleep.	C
Vasomotor/hot flashes	Acupuncture ^{49,91,92,143-148} can be considered for improving hot flashes.	C
	Soy ¹⁴⁹⁻¹⁵¹ is not recommended for hot flashes in patients with BC due to lack of effect.	D

Abbreviations: BC, breast cancer; MBSR, mindfulness-based stress reduction. ^aThe clinical population is patients with BC 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?" ^bDefinitions of the grade of recommendations are as follows¹⁰: 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).

TABLE 2. Training and Licensure Information for A-Grade and B-Grade Integrative Therapies

MODALITY OR THERAPY	TRAINING	LICENSURE AND REGULATION	PROFESSIONAL SOCIETIES AND ORGANIZATIONS
Acupuncture, electro-acupuncture, and acupressure	<p>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 examinations. The Accreditation Commission for Acupuncture and Oriental Medicine (ACAOM) accredits schools of Asian medicine in the United States. Degrees include the Masters of Acupuncture, requiring a minimum of 3 y and 1900 h of training, and the Masters of Acupuncture and Oriental Medicine, requiring a 3-4 y program, averaging 2700-3465 h of training.</p> <p>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.</p> <p>Advanced degrees require a Masters-level degree with additional 1000+ h of training. NCCAOM offers acupuncture and herbal and Oriental medicine certifications on a national level.¹⁵²</p>	<p>UNITED STATES: Acupuncture, Chinese herbology, and Oriental medicine are regulated via state licensing bodies. The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) reports that 44 states plus the District of Columbia have acupuncture practice acts. Forty-three 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 certification. A subset of states regulates acupressure under acupuncture or massage regulations.</p> <p>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.</p>	<p>ACAOM, acaom.org; NCCAOM, mx.nccaom.org</p> <p>College of Traditional Chinese Medicine Practitioners and Acupuncturists of British Columbia (CTCMA), ctcma.bc.ca; College of Traditional Chinese Medicine Practitioners and Acupuncturists of Ontario (CTCMPAO), ctcpao.on.ca; College and Association of Acupuncturists of Alberta (CAAA), acupuncturealberta.ca; Association of Acupuncturists of Quebec (AAQ), acupuncture-quebec.com/en/home.html; Newfoundland and Labrador Council of Health Professionals (NLCHP), nlchp.ca</p>
Hypnosis	<p>Mental health and medical professionals typically practice hypnosis as a specialty or subspecialty. 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, and chiropractor, among many others, prior to obtaining training in hypnosis.</p> <p>Currently, there are no accredited schools offering standard college or university degrees in hypnosis; therefore, training in one of the above professions is typically required before 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 h of classroom and clinical training before certification.</p>	<p>UNITED STATES: To be certified as a clinical hypnotherapist, applicants typically require anywhere from 50 to 200 h of training and often y 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 (ahcp.org/hypnosis-regulation.htm). Typically, clinical hypnotherapists must renew their certification every 2 to 4 y and must have completed 20+ h of approved training during that time.</p> <p>CANADA: Certification is similar to the United States; however, requirements are much higher, between 225 and 1100 h (archcanada.ca/).</p> <p>The Council of Professional Hypnosis encompasses many professional societies and organizations listed (copho.com/org.htm).</p>	<p>Association of Registered Clinical Hypnotherapists (ARCH), archcanada.ca/; American College of Hypnotherapy at the American Institute of Health Care Professionals, ahcp.net/american-college-of-hypnotherapy/; American Society of Clinical Hypnosis (ASCH), asch.net; Hypnosis Motivation Institute (HMI), hypnosis.edu; National Board for Certified Clinical Hypnotherapists (NBCCH), naboard.com; The International Society of Hypnosis (ISH), ishypnosis.org/; Society for Clinical and Experimental Hypnosis (SCEH), skeh.us/; The Milton H. Erickson Foundation, erickson-foundation.org/</p>
Massage	<p>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, must have completed 500 approved educational h or be certified through the National Certification Board for Therapeutic Massage and Bodywork (NCTMB). Licensed nurse and physical therapists may qualify for membership at either the certified or professional level with a minimum of 50 h of additional massage therapy training. Board certification is the highest voluntary credential attainable to massage therapists and bodyworkers in the profession today (for the requirements of board certification, see nctmb.org board-certification).</p>	<p>UNITED STATES: Massage therapy is regulated by some US states. See link for state-by-state massage licensure information (massagetherapy.com/careers/stateboards.php).</p> <p>CANADA: Massage therapists can only be registered, not licensed, in Canada. Currently, only 4 provinces regulate massage therapists: Ontario, British Columbia, New Brunswick, and Newfoundland. The Web site for the Ontario Massage Therapists has links to the 4 provinces' registration procedures and links to other provincial massage organizations.</p>	<p>American Massage Therapy Association, amtamassage.org; ABMP, abmp.com; NCTMB, nctmb.org; Society for Oncology Massage, s4om.org/</p> <p>Massage Therapists' Association of Ontario, secure.rmtao.com/message_therapy/regulation_of_mt/message_therapy_in_canada.htm</p>

TABLE 2. Continued

MODALITY OR THERAPY	TRAINING	LICENSURE AND REGULATION	PROFESSIONAL SOCIETIES AND ORGANIZATIONS
Meditation	<p>Mindfulness-Based Stress Reduction: The Center for Mindfulness in Massachusetts provides meditation specialist training (umassmed.edu/cfm/training/detailed-training-information/teacher-certification-review).</p> <p>The University of California at San Diego Center for Mindfulness provides extensive training (mbpti.org).</p> <p>The University of Bangor in Wales awards a Masters in Mindfulness and also has a range of teacher training programs (bangor.ac.uk/mindfulness/courses.php.en)</p> <p>The Centre for Mindfulness Studies in Toronto, Ontario, Canada, offers 1-d workshops as well as intensive professional training in Mindfulness-Based Cognitive Therapy (mindfulnessstudies.com).</p>	<p>In both the United States and Canada, board certification is the highest credential attainable for meditation teachers in the health care profession today. There is no registration or licensure currently available.</p> <p>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.</p>	<p>American Mindfulness Research Association, goamra.org/</p>
Music therapy	<p>A professional music therapist holds a bachelor's degree or higher in music therapy from one of over 70 American Music Therapy Association-approved college and university programs. Music therapists who currently hold professional designation are listed on the National Music Therapy Registry and are qualified to practice music therapy.</p>	<p>Music therapists are regulated by some US states (eg, North Dakota, Nevada; for state-by-state massage licensure information, see cbmt.org/examination/state-licensure/).</p> <p>Currently no Canadian provinces/territories license or regulate music therapists.</p>	<p>The Certification Board for Music Therapists (CBMT), cbmt.org/; Canadian Association for Music Therapy (CAMT), musictherapy.ca/</p>
Relaxation and stress management	<p>Relaxation and stress management are usually provided by trained mental health professionals, such as registered/chartered/counseling psychologists, psychiatrists, marital and family counselors, clinical social workers, and nurses. Any of these professions could have specific training in these 2 modalities.</p>	<p>Typically, the aforementioned professionals would take courses in relaxation training or stress management as part of their training.</p>	<p>Every jurisdiction has a college of psychologists and social workers. American Psychological Association (APA), apa.org/; Canadian Psychological Association (CPA), cpa.ca</p>
Yoga	<p>There are very stringent criteria to be a yoga instructor, and most jurisdictions have their own requirements. Most jurisdictions have criteria in place 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 United States and Canada, the Yoga Alliance is the biggest body that registers teachers (yogaalliance.org/Credentialing/Credentials_for_Teachers, yogaalliance.org/Credentialing/CredentialsforSchools, and canadianyogicalliance.com).</p>	<p>There are currently no states or Canadian provinces/territories that regulate or license yoga.</p>	<p>Most states and provinces have a professional association (or more than one) for certified yoga instructors.</p>

Acupuncture

Acupuncture involves the stimulation of specific points, (ie, acupoints) by penetrating the skin with thin, solid, metallic needles.^{154,155} A variation of acupuncture includes electroacupuncture, in which a small electric current is passed along acupuncture needles to provide a stronger stimulus than acupuncture alone, with distinct effects suggested by functional magnetic resonance imaging.^{156,157} Acupuncture has been practiced in Asia for thousands of years as a component of traditional medicine systems (eg, 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. Traditional Chinese acupuncture, which is commonly used in North America, requires needle manipulation to produce a *de qi* sensation (a soreness, fullness, heaviness, or local area distension^{157,158}), along with a period of rest with the needles in place.¹⁵⁹ It is posited that this removes 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.¹⁶⁰ Acupuncture practice typically requires formal education through schools, training programs, and certifications (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 America is regulated by some US states and Canadian provinces and territories (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.¹⁶¹ 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). Typically, it is applied topically or ingested in the form of a clear, thick gel.¹⁵³ Aloe vera gel is found in multiple skin products, such as lotions, creams, and sunblock, and is used as a topical ointment to heal wounds, sunburn, insect bites, and skin conditions, including psoriasis and frostbite.¹⁶² In oncology, it is typically used with the goal of healing surgical wounds or preventing or treating radiation-induced dermatitis.

Ginger

Ginger (*Zingiber officinale*) comes from the rhizome or root of a tropical plant with green-purple flowers and an aromatic stem.^{153,163} 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 patients with cancer, it has been studied for the treatment of CINV. Ginger is available in capsule form, fresh as a root, as a tea, as a candy, or at highly diluted quantities in ginger ale. Ginger supplementation should not be used in perioperative settings or in patients with bleeding disorders due to a potential risk of increased bleeding.¹⁶²

Ginseng

Ginseng is derived from a plant root and has been used to treat certain medical problems.¹⁵³ Two common types of ginseng are used: Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*). Another herb called Siberian ginseng or eleuthero is not a true ginseng.¹⁶² 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 and in creams and other products for topical use. Taken as an herbal supplement, ginseng is often used to treat cancer-related fatigue.¹⁶² 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.¹⁶²

Glutamine

Glutamine is a nonessential amino acid used in the biosynthesis of proteins and is primarily synthesized in skeletal muscle.¹⁶² Most of the glutamine synthesized in the body is used by the intestinal tract. Glutamine has numerous biologic functions, including protein and lipid synthesis and the regulation of acid-base balance in the kidney, and it is an important mitochondrial cellular energy source. Normally, the body can synthesize its own glutamine; however, during a critical illness like cancer, not enough glutamine is made, leading to problems such as fatigue and muscle wasting. Glutamine has been used as an oral supplement in patients with cancer to reverse cachexia in those who have advanced disease. It has also been used for CINV in patients with cancer. Glutamine can be obtained from food or supplements, and important food sources include beef, pork, chicken, fish, eggs, milk, dairy products, wheat, cabbage, beets, beans, spinach, and parsley.¹⁶²

Guarana

Guarana is an herbal supplement from the guarana plant (*Paullinia cupana*), which is native to the Amazon basin.¹⁶² Guarana supplements contain 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.¹⁶² 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.^{93,94} 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 in patients with cancer to improve QOL, 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.¹⁵³ When the cream is applied, the hyaluronic acid adheres to injured tissue, provides hydration to the skin, and protects against dehydration and chemical and mechanical irritation. Hyaluronic acid cream is often used by patients with cancer 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.¹⁶⁴ The hypnotic state is obtained by first relaxing the body and then shifting attention toward a narrow range of objects or ideas given by the hypnotist or hypnotherapist. A person under hypnosis may feel more calm and relaxed. In patients with cancer, hypnosis is often used to help relieve stress, anxiety, and pain.

Laser therapy

Low-level laser therapy has been cleared by the FDA to treat lymphedema after breast cancer surgery¹⁶⁵ and should be administered by trained users. It is believed that low-level laser therapy stimulates macrophages and the immune system and breaks down scar tissue, thus improving lymphatic flow.¹⁶⁶

Manual lymphatic drainage and compression bandaging

Manual lymphatic drainage and compression bandaging are used individually and in combination for the treatment of lymphedema after breast cancer surgery.¹⁶⁶ Manual lymph drainage is a specific type of therapeutic massage that ideally is delivered by a health professional who is certified in the technique. Manual lymph drainage can decrease lymphedema when administered early, before symptoms advance.¹⁶⁶

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 the individual.¹⁶⁶

Massage

There are many different forms of this type of physical therapy, which involves a therapist stroking, kneading, applying friction, and stretching specific muscles and other connective tissues at an even tempo with various levels of pressure.¹⁶⁷ In patients with cancer, the goal of massage is to promote relaxation, address muscle stiffness and pain, and resolve musculoskeletal complaints. There are multiple forms of massage, including, but not limited to, Swedish, Shiatsu, and deep-tissue massage. Massage therapists should take precautions with all patients who have cancer and to avoid massaging specific vulnerable areas of the body, including open wounds, bruises, skin breakdown, a blood clot in a vein, a tumor site, areas near a medical device (eg, drain), or sensitive skin after radiation therapy.¹⁶⁸ In addition, certain patients with multiple bone metastases may be at risk for fracture during deep massage. The practice of massage therapy in North America is regulated by some US states and Canadian provinces and territories (Table 2).

Meditation

Meditation is a group of self-regulation practices focused on training attention and awareness to bring mental processes under greater voluntary control.¹⁶⁹ In patients with cancer, 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 its application. Most meditation practices have 4 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.¹⁷⁰ The focus of attention may be on a specific target, such as the breath or a repeated sound or mantra (known as *concentration meditation*); on all experiences that enter the field of awareness (called *open awareness* or *mindfulness meditation*); or a combination of both. There has been growing interest in cancer care on the practice of a secular form of mindfulness meditation called *mindfulness-based stress reduction* (MBSR), which is based on the work of Jon Kabat-Zinn.¹⁷¹ MBSR is typically delivered in an 8-week, structured group program consisting of a range of meditation practices, including a sensate focus body scan, sitting meditation, walking meditation, loving-kindness practice, and gentle Hatha yoga postures. All formal practices are designed to cultivate increasing levels of mindfulness in day-to-day life. Participants engage in home practice daily

throughout the program, and each session involves teaching relevant concepts, discussions of progress and barriers to practice, and introduction and practice of new meditation modalities. Several recent articles and meta-analyses have reviewed the literature on the use of MBSR in the oncology setting, and some are specific to breast cancer.¹⁷²⁻¹⁷⁵

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.¹⁷⁶ Mistletoe is a parasitic plant from the Santalaceae family that attaches to and penetrates the branches of a tree or shrub to absorb water and nutrients from the host plant. The use of mistletoe as a medicine extends back centuries, whereas its modern use for cancer care was promoted in Europe, and particularly in Germany, in the early part of the 20th century.¹⁷⁷ There are 3 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 common internationally prescribed substances in outpatient clinics for cancer, where they are delivered most often as a subcutaneous injection or occasionally as an intravenous infusion.¹⁷⁸ While this therapy is often used clinically for its antineoplastic potential, clinical trial evidence on the use of mistletoe is based on trials in which it is coadministered with conventional treatments to improve QOL.¹⁷⁸

Music therapy

Music therapy is the clinical use of music to accomplish individualized goals within a therapeutic relationship by a credentialed professional.¹⁷⁹ In cancer care, music therapy is used to address various physical, emotional, cognitive, and social needs. Qualified music therapists assess patients' 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* (eg, listening to music before a medical intervention) or *active* (eg, a 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 physiologic pathways.^{180,181} The practice of music therapy in North America is regulated by some US states (Table 2).

Reflexology

In reflexology, a trained practitioner applies pressure to the feet, hands, ears, and face using specific thumb, finger, and

hand techniques with the goal of stimulating the reflex areas to promote physiologic changes 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 to help numerous health problems.¹⁸² 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 QOL.

Relaxation techniques

Various techniques are used to promote relaxation in patients with cancer. The NCI defines relaxation techniques as including progressive muscle relaxation (PMR), guided imagery, autogenic training, biofeedback, self-hypnosis, and deep breathing exercises.¹⁸³ PMR focuses on the tightening and relaxation of specific, successive muscle groups and is usually combined with breathing and imagery exercises.¹⁸³ 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.¹⁸³ Autogenic training involves concentrating on physical sensations of warmth, heaviness, and relaxation in different parts of the body.¹⁸³ Biofeedback uses electronic devices to monitor and teach control of certain bodily functions, such as breathing or heart rate, to facilitate relaxation.¹⁸³ Self-hypnosis refers to training patients to induce a hypnotic state, which is a natural state of aroused, attentive, focal concentration along with a relative suspension of peripheral awareness, either on their own or when prompted by a phrase or a cue.¹⁸³ Deep breathing exercises involve the use of slow, deep, and even breaths, sometimes called diaphragmatic or belly breathing.¹⁸³

Qigong

The word qigong consists of 2 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.¹⁸⁴ 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.¹⁸⁴ In patients with cancer, qigong is often used to reduce anxiety, fatigue, and pain; to support the immune system; and to 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,¹⁸⁵

including after a cancer diagnosis, during cancer treatment, and throughout 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.¹⁸⁵ To address stress and induce the relaxation response, stress-management programs teach techniques like 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.^{186,187} Participants are taught coping skills and practice various techniques for cognitive reappraisal. One common structured group stress-reduction program studied in oncology is called *cognitive-behavioral stress management*.^{140,188} 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 years and more recently in the American diet.¹⁶² Soybeans are the seeds of the soy plant and contain isoflavones and soy protein. Soy is available as a dietary supplement in tablet or capsule form and contains isoflavones and/or soy protein. Soybeans can be cooked or eaten or may be 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.¹⁶² In patients with cancer, soy is often used to treat hot flashes.

Yoga

Yoga is a mind-body practice with origins in ancient South Asian philosophy and practice.¹⁸⁹ The term yoga is derived from the Sanskrit word *yug*, meaning “yoke” or “union.”¹⁹⁰ 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 is a wide range of yoga forms and styles. The most commonly practiced form of yoga in the United States and Canada is Hatha yoga, which emphasizes

postures (*asanas*) and often breathing exercises (*pranayama*). In patients with cancer, yoga is used for a variety of conditions, including stress, anxiety, depression, and fatigue, and as a method to increase physical activity.

Literature Review on the Use of Complementary and Integrative Therapies for Clinical Outcomes in Patients With Breast Cancer

The clinical outcomes addressed here are common symptoms and side effects experienced by patients with breast cancer during treatment or as sequelae of treatment. The outcomes of interest include: anxiety/stress, pain, depression/mood, fatigue, sleep disturbances, QOL and physical functioning, CINV, radiation dermatitis, vasomotor outcomes, lymphedema, CIPN, pain, and sleep disturbance. Guidelines outlining conventional approaches to managing these symptoms and outcomes have been issued by national organizations like the National Comprehensive Cancer Network and the American Society of Clinical Oncology, but many of the prior guidelines and reviews did not include thorough reviews of complementary and integrative medicine approaches.¹⁹¹⁻¹⁹⁷ This review fills that gap for patients with breast cancer.

Below, for each therapy and clinical outcome of interest that received a grade of A or B, we summarize the trials that contributed to the graded recommendation to give the reader an understanding of the specific interventions that were tested. To provide additional context, there is a brief review of the literature on the use of each 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 grades of C, D, or H, we provide a brief overview of the rationale for the graded recommendation. The supporting tables provide detailed information on each trial that informed an A-graded or B-graded recommendation (see Supporting Information Table 2,²⁶⁻⁴⁸ Supporting Information Table 3,^{26-30,33,35,40-43,45-48,53-56,59,60,69,72-90} Supporting Information Table 4,^{27-29,43,46-48,73-75,82-85,104-106,127,128} and Supporting Information Table 5⁶¹⁻⁶⁵). Table 3 lists the clinical outcomes and integrative therapy combinations that had insufficient evidence to make a grade A, B, C, D, or H recommendation.^{26,33,36,37,40,43,45-50,52,69,72,73,76,77,79,83,84,87-89,94,97,104,108,111,113,129,130,133-135,138,139,149,198-301}

Updated Recommendations

Although the majority of graded recommendations remain the same as those in the previously published guidelines,⁹ there are 5 noteworthy changes. For the outcome of anxiety and stress reduction, the use of meditation moved from grade B to grade A because of results from a fifth trial,²⁶ in

addition to the previously published 4 trials,²⁷⁻³⁰ showing beneficial effects. The use of yoga for depression and mood disturbance was downgraded from grade A to grade B because of 4 new published studies demonstrating conflicting results.^{40,79-81} The use of yoga for improving QOL changed from grade C to grade B, because 2 additional trials demonstrated beneficial effects.^{104,128} Finally, new trials on the use of yoga^{40,80,104} and hypnosis^{97,98} for fatigue upgraded previous recommendations from grade I to grade C.

Use of Integrative Therapies for Anxiety/Stress Reduction

Description of anxiety/stress

Patients with cancer may experience stress related to the life changes associated with a cancer diagnosis, both during and after treatment. Under the NCI's Common Terminology Criteria for Adverse Event (CTCAE) psychiatric disorders, anxiety is categorized 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 QOL.³⁰² 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 patients with breast cancer who report anxiety ranges from 12% to 47%, and approximately 11% to 16% of patients experience combined symptoms of anxiety and depression.³⁰³⁻³⁰⁵ Evidence suggests that effective anxiety management is associated with improvements in QOL, psychological adjustment, understanding of the disease, decision making, and adherence to treatment.³⁰⁶⁻³⁰⁸

Meditation (A grade)

Overview of meditation interventions for anxiety/stress reduction. Meditation is recommended for reducing anxiety in patients with breast cancer, including during radiation therapy (grade A). Many uncontrolled trials have been published, but this recommendation is based on 5 RCTs completed between 2009 and 2013 that used meditation to reduce anxiety symptoms (see Supporting Information Table 2).²⁶⁻³⁰ Anxiety was the primary outcome for 4 of those trials. In all 5 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, 3 types of meditation

interventions were tested. Three trials implemented an intensive, integrated MBSR program customized for patients with breast cancer in which participants were trained in mindfulness meditation and gentle yoga for body awareness.^{26,29,30} A fourth intervention was called the Mindful Movement Program and was also an intensive, integrated program customized for patients with breast cancer 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.²⁷ The fifth trial assessed a brain wave vibration meditation²⁸ or a mind/body training technique that combined simple, rhythmic movements with music, action, and positive messages.²⁶

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; that analysis included 47 trials with 3515 participants.³⁰⁹ Overall, mindfulness meditation programs demonstrated moderate evidence of improved anxiety at 8 weeks and at 3 to 6 months and showed low evidence of improved stress/distress and mental health-related QOL. The findings of these reviews across other patient populations and disease types support our recommendations.

The earliest work in MBSR interventions specifically demonstrated sustained benefits for individuals with anxiety disorders, and more recent research has continued to show a benefit for generalized anxiety.³¹⁰⁻³¹² The first study conducted in patients with cancer, an RCT of 89 patients with a variety of cancer types, found substantial decreases in anxiety for the group that received MBSR compared with results for a usual-care control group; results for the MBSR interventions were maintained at 6-month follow-up.^{313,314} The reduction in anxiety observed in the above-described 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 patients with cancer and cancer survivors; of those 22 studies, 21 included either a substantial percentage of patients with breast cancer or only patients with breast cancer.³¹⁵ Overall, that review included 12 nonrandomized studies and RCTs. In the nonrandomized studies, mindfulness-based therapy was associated with significantly reduced symptoms of anxiety postintervention with a moderate effect size, while the pooled effects sizes of RCTs, including that discussed above,²⁹ resulted in a larger effect size ($P < .001$). Although the review reported that overall study quality

TABLE 3. Clinical Outcomes and Integrative Therapies With Insufficient Evidence to Form a Clinical Recommendation (I-Statement)^a

OUTCOME	INTEGRATIVE THERAPIES
Adherence	Acupressure, ¹⁹⁸ multimodal ¹⁹⁹
Anemia	LCS101 combination botanical, ²⁰⁰ RG-CMH combination botanical, ²⁰¹ shenqi fuzheng injection ²⁰²
Anxiety/stress reduction	Art therapy, ^{203,204} comprehensive coping strategy, ²⁰⁵ electrical nerve stimulation, ²⁰⁶ healing touch, ^{94,207} hypnosis, ²⁰⁸ myofascial release, ²⁰⁹ multimodal, ^{210,211} reflexology, ^{138,139,212} reiki, ²¹³ tai chi ²¹⁴
Cardiomyopathy	N-acetylcysteine ²¹⁵
Chemotherapy-induced nausea and vomiting	Acupressure, ²¹⁶ aromatherapy, ²¹⁷ <i>Agaricus sylvaticus</i> , ²¹⁸ Cocculine (complex homeopathic Rx), ²¹⁹ comprehensive coping strategy, ²⁰⁵ massage, ⁵² Nevasic audio program, ²²⁰ yoga ⁴³
Cognition	Natural environment, ²²¹ <i>Ginkgo biloba</i> , ²²² meditation, ⁷² yoga ²²³
Constipation	Self-management program ²²⁴
Depression/mood	Art therapy, ²⁰³ Biofield Healing, ²²⁵ comprehensive coping strategy, ²⁰⁵ CoQ10, ²²⁶ electrical nerve stimulation, ²⁰⁶ <i>Gandoderma lucidium</i> , ²²⁷ guarana, ¹⁰⁸ hypnosis, ²²⁸ multimodal, ^{199,210,229,230} myofascial release, ²⁰⁹ qigong, ¹³⁵ reflexology, ^{138,139} tai chi ²¹⁴
Fatigue	Acupressure, ¹⁹⁸ acupuncture, ^{50,231,232} Biofield Healing, ²²⁵ comprehensive coping strategy, ²⁰⁵ CoQ10, ²²⁶ <i>Gandoderma lucidium</i> , ²²⁷ light treatment, ²³³ massage, ⁸⁷ meditation, ^{72,76} mind-body cognitive therapy, ²³⁴ movement, ²³⁵ multimodal, ^{230,236,237} multivitamin, ²³⁸ polarity therapy, ^{239,240} stress management, ²⁴¹ qigong, ¹³⁵ reflexology, ¹³⁹ relaxation, ^{242,243} stress management, ³⁶ yoga ^{40,46-48,79,83}
Lymphedema	CYLO 3 FORT, ²⁴⁴ electrotherapy, ²⁴⁵ ginkgo forte, ²⁴⁶ pentoxifyline and vitamin E, ^{247,248} yoga ²⁴⁹
Neuropathy	Omega 3 fatty acids, ²⁵⁰ vitamin E, ^{251,252} acupuncture ¹³⁰
Neutropenia/leukopenia	Cat's claw, ²⁵³ LCS101 combination botanical, ²⁰⁰ RG-CMH combination botanical, ²⁰¹ mistletoe, ^{133,134} shenqi fuzheng injection ²⁰²
Pain	Comprehensive coping strategy, ²⁰⁵ stress management, ³⁶ vitamin D2, ²⁵⁴ electrical nerve stimulation, ²⁰⁶ cognitive and behavioral therapy, ²⁵⁵ hypnosis, ²⁵⁶ massage, ⁸⁸ myofascial release, ²⁰⁹ reflexology ^{139,212}
Quality of life	Acupressure, ²¹⁶ Biofield Healing, ²²⁵ calendula cream, ²⁵⁷ cannabis, ²⁵⁸ chlorella extract, ²⁵⁹ CoQ10, ²²⁶ curcuminoids, ²⁶⁰ electrical nerve stimulation, ²⁰⁶ electrotherapy, ²⁴⁵ flaxseed, ²⁶¹ <i>Gandoderma lucidium</i> , ²²⁷ ginkgo forte, ²⁴⁶ guided imagery, ²⁶² healing touch, ⁹⁴ homeopathy, ²⁶³⁻²⁶⁵ hypnosis, ⁹⁷ laser therapy, ¹¹¹ manual lymphatic draining, ¹¹³ massage, ⁸⁷ meditation, ^{26,72} movement, ²³⁵ music therapy, ⁸⁹ multimodal, ^{199,210,230,236,237,267} multivitamin, ²³⁸ polarity therapy, ^{239,240} relaxation, ^{69,77} shenqi fuzheng, ²⁰² shark cartilage, ²⁶⁸ soy, ¹⁴⁹ supportive-expressive group therapy, ²⁶⁹ tai chi ^{214,270-272}
Physical functioning	Mind-body cognitive therapy, ²³⁴ music therapy, ³³ multimodal, ¹⁹⁹ myofascial release, ²⁰⁹ reflexology, ¹³⁹ stress management, ³⁷ tai chi, ^{270,272} yoga ^{45,79,84,273}
Radiation therapy-induced toxicity outcomes	Adlay bran extract, ²⁷⁴ alpha ointment with henna, ²⁷⁵ Aquaphor-Biafine-Radiacare, ^{276b} boswellia cream, ²⁷⁷ calendula cream, ^{257,278} chamomile, ²⁷⁹ curcumin, ²⁸⁰ glutamine, ²⁸¹ homeopathic pills, ²⁸² honey, ^{283,284} hydration, ²⁸⁵ massage, ²⁸⁶ oil-in-water emulsion, ²⁸⁷ glutathione and anthocyanin gel, ^{288c} wheat grass extract, ²⁸⁹ pentoxifyline and vitamin E ^{290,291}
Sleep disturbance	Acupuncture, ^{49,50,129} calendula cream, ²⁵⁷ meditation, ^{72,292-294} qigong, ¹³⁵ stress-management techniques ³⁶
Vasomotor outcomes	Black cohosh, ^{295,296} flaxseed, ²⁶¹ homeopathy, ^{264,265} hypnosis, ²⁹⁷ magnetic therapy, ²⁹⁸ meditation, ⁷³ peppermint, ²⁹⁹ vitamin E, ³⁰⁰ yoga ^{104,301}

Abbreviations: CoQ10, coenzyme 10Q; CYLO 3 FORT, fluid extract of *Ruscus aculeatus*, hesperidin methyl chalcone, and vitamin C; LCS101, a botanical compound mixture; RG-CMH, a Chinese medicinal herb complex. ^aDefinition 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 US Preventive Services Task Force Recommendation Statement. If the service is offered, then patients should understand the uncertainty about the balance of benefits and harms. ^bSuppliers for these topicals are as follows: Aquaphor (Beiersdorf AG, Hamburg, Germany), Biafine (Laboratoire Medix, Houdan, France), and RadiaCare (Medline Industries, Inc., Northfield, IL). ^cRayGel is a proprietary glutathione and anthocyanin gel.

varied among the 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 patients with breast cancer and in breast cancer survivors. Another review of 9 studies (including 2 RCTs, a quasi-experimental case-control study, and 6 single-group pre/post-intervention studies) investigated the efficacy of MBSR

on mental health specifically in patients with breast cancer and found an overall decrease in anxiety scores after MBSR ($P < .01$).¹⁷⁴ That 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 (MBIs) on anxiety and distress in cancer.^{174,175,316}

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.^{317,318} Typically, potential participants are screened through individual orientation interviews before joining meditation group programs, and participants who have serious mental health issues are often redirected to individual counseling or psychiatric intervention before or concomitant with MBI participation. Group facilitators are typically mental health care professionals trained to identify and manage psychological symptoms and reactions that may occur during the training.

Participants in these meditation therapy groups typically report that the sessions are enjoyable, and dropout rates are often low and are comparable to the rates in other psychosocial group programs. Because they are offered in group settings, meditation interventions are more cost effective than traditional individual counseling or psychotherapy 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 MBIs. Hence, the specificity of meditation therapy is not yet known. With the exception of the trial reported by Carlson et al,²⁶ studies have not compared MBIs 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,^{313,319} in that participants who practice more at home often benefit more, but this area is still being investigated.³²⁰ 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 al³²¹ demonstrated that an online, live MBI group in which rural and remotely located patients who had cancer participated weekly over 8 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 that 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 postsurgery (grade B) based on results from 5 RCTs comparing music therapy interventions with standard care (see Supporting Information Table 2).³¹⁻³⁵ Study participants included patients with breast cancer who were 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,^{31,32,34,35} including reducing sedation requirements during radiation therapy (measured as a secondary outcome).^{31,32,34} The fifth trial, which was conducted by Hanser et al,³³ examined active music therapy (which required active engagement of the participant) and yielded substantially different results from the 4 trials of passive music therapy. In that 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 (eg, listening to music).

A recent systematic review and meta-analysis by Boehm et al³²² assessed the effect of different expressive therapies, including passive and active music therapy, on improving anxiety, depression, and QOL in patients with breast cancer. The review included 3 of the RCTs that formed the basis for our recommendation of passive music therapy for anxiety/stress reduction, of which 2 trials tested passive music therapy,^{31,34} and the other tested active music therapy.³³ Another recent meta-analysis included an additional RCT evaluating art therapy.²⁰⁴ Boehm et al found a clinically and statistically significant mean difference ($P < .01$) in the anxiety scores of patients who received music therapy compared with the control group,³²² 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 adult women in a clinical cancer setting.³²³

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 for patients with breast cancer 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 the long-term effects of passive music therapy on anxiety, because 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 versus active music therapy on anxiety are needed to clarify whether the benefit is because of 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 4 RCTs, which were completed between 2008 and 2013 among patients with breast cancer, testing a stress-management intervention compared with usual care using an improvement in anxiety as the primary outcome.³⁶⁻³⁹ Study participants included only patients who had breast cancer in 2 of the 4 trials^{36,39} and a mixed group of patients with cancer that included a significant proportion of women who had breast cancer in the other 2 trials.^{37,38} In all 4 trials, patients with breast cancer were included from defined periods along the continuum of care, including before surgery, during chemotherapy, and after cancer treatment. Patients thus were 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 4 trials, 2 indicated that the improvement was statistically significantly different compared with the control group.^{37,39} One trial found a similar improvement in both the intervention and control groups with no statistically significant differences across groups,³⁶ and the fourth trial found no improvement³⁸ (see Supporting Information Table 2, Stress Management).

Stress-management interventions varied among the studies (see Supporting Information Table 2).³⁶⁻³⁹ One trial³⁸ implemented a self-administered stress-management intervention before patients received chemotherapy. The intervention included video and booklet information specific to stress management and exercise and was delivered by a doctoral-level psychologist.³⁸ A second trial³⁶ 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 from 45 to 60 minutes each and

took place in the hospital.³⁶ The stress-management portion included information, demonstrations and instructions for paced breathing, PMR with guided imagery, and the use of coping strategies to manage stress. A third trial,³⁷ which took place at a multicenter community clinical oncology program involving 20 clinical sites, was designed to determine whether a self-administered stress-management intervention that was previously identified as beneficial for patients with cancer would improve QOL 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, combined stress-management and exercise training, and usual care. Patients assigned to stress-management training were provided written materials and videos on 3 techniques, including PMR and guided imagery, abdominal breathing, and coping skills training.³⁷ A fourth trial³⁹ 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 nonmetastatic 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 from heterogeneous cancer populations that included 6 studies of breast cancer-only samples.³²⁴ The interventions assessed were all structured and included counseling and coping components in addition to some interventions, including PMR, 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. Because the majority of trials discussed above tested long-term interventions, the guideline recommendation is specific to long-term stress-management programs. However, this may be complicated by other factors, including a potential increase in the cost of delivery for providers/facilitators as a result of the implementation of longer term programs, and it also could present a barrier to patients who have 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 patients with breast cancer.

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

Yoga (B grade)

Overview of yoga interventions for anxiety/stress reduction. Yoga is recommended for reducing anxiety in patients with breast cancer (grade B). This recommendation is based on 9 RCTs, completed between 2007 and 2014, in which a yoga intervention was implemented to reduce physical symptoms and psychological distress, including anxiety, which was assessed as the primary outcome in 4 of the studies (see Supporting Information Table 2).⁴⁰⁻⁴⁸ Those 9 trials tested 5 different yoga interventions. The first intervention was an intensive, integrated yoga program customized for patients with breast cancer, 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*).⁴¹⁻⁴⁴ A second intervention implemented Iyengar yoga, a traditional form of Hatha yoga emphasizing 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).⁴⁵ A third intervention used Patanjali's yoga sutras, which included warm-up movements synchronized with breathing, selected postures, deep relaxation techniques, alternate-nostril breathing (*pranayama*), and meditation.⁴⁸ 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.⁴⁰ Pranayama or yoga breathing practices were tested in the remaining trials.^{46,47} Study participants included women who had been recently diagnosed with breast cancer, those who were currently receiving 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.³²⁵⁻³²⁸ The first meta-analysis investigating the impact of yoga interventions on psychological health outcomes³²⁹ identified 10 articles that examined outcomes in patients with breast cancer ($n = 7$ articles), patients with lymphoma ($n = 1$), and mixed cancer

populations ($n = 2$). Analyses involving 8 trials that assessed anxiety found that lower anxiety was associated with the yoga groups relative to controls ($P = .009$); and similar results with yoga interventions were observed for distress ($P = .003$) and stress ($P = .006$). However, because this was a heterogeneous sample of patients, it was unclear whether the results could be generalized specifically to patients with breast cancer. More recently, a systematic review and meta-analysis assessing the impact of yoga interventions on QOL and psychological health specifically in patients with breast cancer and survivors was conducted.³³⁰ Overall, 12 RCTs 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 ($P < .01$), perceived stress ($P = .03$), and psychological distress ($P < .01$). However, it is 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 stated that, based on these positive preliminary results, a wide variety of yoga practices could be recommended for this population.³³⁰ Finally, although the methodological quality across the trials varied, it has been demonstrated that yoga is beneficial for reducing psychological distress in a wide variety of non-cancer clinical populations, including adult patients with anxiety and depression.^{331,332}

Risk/benefit assessment of yoga interventions. Yoga interventions are noninvasive and, with proper instruction, can be adapted to people who have functional and other impairments without harm. Yoga interventions are low cost and can be practiced at home with instructional videos; however, in the context of breast cancer, they are best undertaken under the guidance of certified yoga instructors who have specific training in teaching patients with cancer and cancer survivors. Such programs also have the ability to be adapted and modified for people with medical conditions or limited mobility.³³³ 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 the 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, because many of these studies are small and preliminary. Furthermore, the studies summarized above have some inconsistency of results; the trials from India⁴¹⁻⁴⁴ reported consistently positive results, while the trials from North America^{40,45-48} 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 QOL measures. Future trials of yoga interventions for anxiety/stress reduction should focus on testing forms of yoga that can be more easily applied and, to improve the generalizability of the results, should test the interventions in larger sample size and in minority and underserved populations that may not have easy access to yoga programs.

C-graded therapies for anxiety and stress reduction

Acupuncture,⁴⁹⁻⁵¹ massage,⁵²⁻⁵⁵ and relaxation⁵⁶⁻⁶⁰ can be considered for reducing anxiety and stress (grade C). Three high-quality trials assessed acupuncture for anxiety and stress reduction, which were secondary outcomes; 2 of the 3 positive trials were small,^{49,50} and the other demonstrated no effect.⁵¹ However, of 4 studies that examined massage for anxiety, 3 with positive findings included fewer than 40 participants,⁵²⁻⁵⁴ and the other demonstrated no effect.⁵⁵ Results were inconclusive regarding relaxation for anxiety and stress reduction because of inconsistencies and small sample sizes. Future directions in research can focus on evaluating 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.³⁰² The CTCAE categorizes depression as a psychiatric disorder on a scale from 1 (mild) to 5 (death). Symptoms of depression in patients with cancer 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 patients with breast cancer reporting depression ranges from 3% to 34%, and 11% to 16% of patients experience combined depression and anxiety symptoms, depending on the population studied.³⁰³⁻³⁰⁵ Effectively managing depression may improve QOL, psychological adjustment, understanding of the disease, decision making, adherence with cancer treatment, and response to cancer treatment.³⁰⁶⁻³⁰⁸

Meditation (A grade)

Overview of meditation interventions for depression/mood disturbances. Meditation, particularly MBSR, is recommended for treating mood disturbance and depressive symptoms in patients with breast cancer (grade A). This recommendation is based on 10 RCTs, completed between 2009 and 2015, that used meditation to help reduce depressive symptoms (see Supporting Information Table 3).^{26-30,72-76} Depression was the primary or secondary outcome for all of these trials. In 8 of the 10 trials,^{27-30,72-74,76} a meditation intervention was compared with a usual care group, a waitlist control group, or another active intervention; 2 other trials used a 3-arm trial design.^{26,75} 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 ages 55 years and older. The study sample sizes ranged from 33 to 336 participants and tested 6 different types of meditation interventions, including an intensive, integrated MBSR program customized for patients with breast cancer^{26,29,30,73,75}; the Mindful Movement Program⁷³; brain wave vibration meditation²⁸; Tibetan sound meditation⁷²; cognitively based compassion training⁷⁶; and Transcendental Meditation.⁷⁴

In the meta-analysis examining the effect of mindfulness-based therapy on psychological outcomes in adult cancer populations,³¹⁵ compared with results in controls, mindfulness-based therapy was associated with significantly reduced depression postintervention, with a moderate effect size in the nonrandomized studies and RCTs, including one trial listed above²⁹ ($P < .001$). By using evidence from 9 well conducted studies, the review and meta-analysis by Zainal et al confirmed the use of mindfulness-based therapies for the management of depression in patients with breast cancer and survivors despite the heterogeneity in the reviewed studies; the results of the meta-analysis identified a significant pooled effect size for MBSR on depression scores (effect size, 0.575; 95% confidence interval, 0.429-0.722 [$P < .01$]).¹⁷⁴ In their study, Teasdale et al³³⁴ modified traditional MBSR by combining it with principles of cognitive behavioral therapy to create mindfulness-based cognitive therapy, which was designed specifically to prevent recurrence of depressive symptoms in individuals with relapsed major depression.³³⁵ The intervention proved effective for preventing depression relapse³³⁴ and has since been widely applied and adapted to treat depression symptoms in a range of clinical samples.³³⁶ In patients with cancer, other RCTs of meditative interventions resulted in decreased depressive symptoms,³¹³ with results maintained after 6 months of follow-up.³¹⁴ The reduction in depressive symptoms observed in the above-described 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 outcomes. Despite these limitations, the evidence suggests that meditation and MBSR could be added to treatment plans or 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 effects of specific meditation techniques on specific mental health outcomes.

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 6 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 (see Supporting Information Table 3).^{56,59,60,69,77,78} Five of the 6 trials measured depression as the primary outcome. In all 6 trials, a relaxation therapy intervention group was compared with a standard care group. The interventions comprised some form of relaxation therapy that included PMR and guided imagery or visualization techniques. One trial⁵⁶ assessed autogenic training, which provided training in relaxation 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.⁷⁸ Participants in these studies included patients with breast cancer who had undergone 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 patients with breast cancer. Thus, a review specific to relaxation interventions that includes PMR and guided imagery for depression/mood or other psychological outcomes in patients with breast cancer

and survivors is warranted. A review of studies of guided imagery as adjuvant cancer therapy broadly assessed 6 RCTs and found the methodological quality inconsistent.³³⁷ 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, the results indicated that guided imagery as a sole adjuvant cancer therapy was supportive and increased comfort in patients and had few risks.

Beyond decreasing depression, relaxation therapy may also have a beneficial impact on other symptoms important to women with breast cancer. For instance, PMR was effective in ameliorating sleep problems and fatigue in women undergoing chemotherapy for breast cancer.³³⁸ Other likely benefits attributable to this therapy in breast cancer populations include reduced nausea and anxiety.^{339–342}

Risk/benefit assessment of relaxation interventions. Relaxation therapy is noninvasive 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 the ability to decrease depression in adults^{343,344} and depression associated with cardiac disease.³⁴⁵ The minimal cost and low potential for harm with relaxation therapy, in conjunction with its evidence of benefit, support an 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.

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 from 15 RCTs, completed between 2006 and 2015, that used a yoga intervention to reduce physical symptoms and psychological distress, including depression (see Supporting Information Table 3).^{40-43,45-48,79-85} 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 receiving 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 in size from 23 to 200 participants. Five trials assessed an intensive, integrated yoga program that was customized for patients with breast cancer, including asanas, pranayama, and yoga nidra.^{41-43,81,85} Five trials implemented Iyengar yoga, a traditional form of Hatha yoga, and passive backbends.^{45,80,82-84} Two trials assessed Patanjali's yoga sutras, which included warm-up movements synchronized with breathing, selected postures, deep relaxation techniques, meditation, and alternate-nostril breathing (pranayama)^{48,79}; while 2 trials evaluated only the pranayama practices.^{46,47} 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.⁴⁰

It has been shown that yoga is beneficial for reducing depression in a wide variety of clinical populations,^{332,346-348} and specifically among individuals with cancer.³²⁵⁻³²⁸ One meta-analysis investigating the impact of yoga interventions on psychological health outcomes³²⁹ analyzed 8 trials of yoga interventions for depression and showed improvement in depressive symptoms in the yoga groups compared with the control groups ($P = .002$) among a heterogeneous sample of patients. Specifically in patients with breast cancer and in breast cancer survivors, a meta-analysis³³⁰ of 12 RCTs, representing a total of 742 participants, revealed short-term effects of yoga interventions on improved psychological health, including depression ($P < .01$). 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 stated 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, because findings differ between populations from India^{41-43,85} and North America.^{45,46,48,82-84} Despite these limitations, the evidence suggests that yoga interventions could be added to treatment plans or 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.³³³

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 various degrees and types of mood disturbances and depression in addition to including larger sample sizes and testing across active controls.

Massage (B grade)

Overview of massage therapy interventions for depression/mood disturbances. Massage therapy is recommended to improve mood disturbance in breast cancer survivors after active treatment (ie, surgery, chemotherapy, radiation; grade B). This recommendation is based on results from 6 trials completed between 2004 and 2012.^{53-55,86-88} In the trial reported by Listing et al,⁸⁷ the primary outcomes focused on physical discomfort and fatigue, with mood disturbance as a secondary outcome. The other 5 trials assessed depression as the primary outcome and had other secondary outcomes, including perceived stress, QOL, pain, heart rate variability, and emesis. In the 5 trials, the effect of massage therapy was compared with the effect of standard care. The studies, which took place in the United States,⁵³ Germany,^{54,86,87} England,⁵⁵ and Spain,⁸⁸ all included breast cancer survivors who had completed active cancer treatment at least 3 months before study enrollment. The study sample sizes ranged from 20 to 288 participants. In 3 of the 6 trials, the massage therapy intervention was a variation of classic massage involving rhythmic stroking, kneading, and acupressure at select areas on the body.^{54,86,87} The study by Fernandez-Lao used an experienced and trained physical therapist to administer manual massage therapy.⁸⁸ Wilkinson et al⁵⁵ included aromatherapy as part of the massage therapy, which was individualized across study participants. Hernandez-Reif et al⁵³ 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 biweekly, 30-minute massages for 5 weeks,^{54,86,87} with the exception of the trial by Fernandez-Lao et al, in which a one-time, 40-minute massage session was assessed.⁸⁸ Across these studies, compared with control

groups, women in the intervention groups 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 by Fernandez-Lao et al, the improvements in depression outcomes with a single-session massage intervention depended on the participant's individual level of enthusiasm for that intervention. The classic massage studies^{54,86,87} and one trial that combined massage with aromatherapy⁵⁵ found that the massage interventions significantly decreased depression only immediately after the intervention but not long term. The remaining study that combined massage therapy with acupressure and Trager⁵³ 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 QOL, including measures of depression.³⁴⁹ In total, 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 8 trials, 3 of which are summarized in this section,^{53,54,87} did not find significant beneficial effects of massage therapy for depression. However, that meta-analysis was limited by significant heterogeneity across the studies that assessed depression as the outcome ($P = .002$) as well as by small and possibly underpowered sample sizes, which may have accounted for the nonsignificant 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.³⁵⁰

Risk/benefit assessment of massage therapy interventions. Classic massage is a noninvasive therapy that has limited adverse effects. For patients with cancer, 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.³⁵¹ Since trained, licensed therapists delivered the interventions tested in these studies, the recommendation of massage for depression applies specifically to massage by trained therapists.^{352,353} Some caution is needed, however, for individuals receiving anticoagulation therapy because of 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 because of 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.³⁵⁴ However, a more recent (2010) meta-analysis of 17 RCTs concluded that massage therapy had a positive effect on individuals suffering from depression.³⁵⁵ 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 patients with breast cancer. 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.

Music therapy (B grade)

Overview of music therapy interventions for depression/mood disturbances. Passive music therapy is recommended to improve depression/mood disturbances in patients with newly diagnosed breast cancer (grade B). This recommendation is based on 4 RCTs, completed between 2000 and 2011, that tested a music therapy intervention to improve mood/depression (see Supporting Information Table 3).^{33,35,89,90} Depression/mood disturbances were assessed either as the primary outcome or as a secondary outcome to anxiety. In all 4 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 with controls,^{35,89,90} and the fourth trial examining active music therapy³³ 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 that were not sustained over time.

Therefore, the guideline recommendation is specific to passive music therapy.

Of the 5 studies combined in the meta-analysis described above that assessed multiple types of art therapies for improving anxiety, depression, and QOL among patients with breast cancer³²² (4 music therapy interventions, including 2 trials identified in our review,^{33,204} and an art therapy trial), a clinically and statistically significant mean difference ($P = .05$) was observed across all depression scores in the music therapy intervention groups compared with control groups. Furthermore, a systematic review of music therapy specifically for depression in the *Cochrane Database of Systematic Reviews* found that, although only 5 RCTs have tested music therapy interventions for depression and have 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.³⁵⁶ 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 patients with breast cancer is the same as that 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 were limited to assessing short-term improvement of mood/depression after breast cancer treatments or during metastatic cancer diagnosis. In addition, studies should attempt to replicate the null findings of active music therapy interventions 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 above (see Use of Integrative Therapies for Anxiety/Stress Reduction).

C-graded therapies for depression/mood

Acupuncture,^{49-51,91,92} healing touch,^{93,94} and stress management^{36-38,95,96} can be considered for improving mood and depressive symptoms (grade C). Five trials assessed acupuncture as a treatment for depression/mood (but as a secondary outcome), and only one trial was large,⁵¹ 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 effect⁹⁴ and a larger study showing a positive effect.⁹³ Although 5 large studies were reviewed for the effect of stress management on depression/mood, the findings were inconclusive because of inconsistent results across trials. Future research directions should

include conducting trials with larger samples sizes and replicating trials with these modalities to examine their impact on depression symptoms and improving mood as the primary outcome.

Use of Integrative Therapies for Fatigue

Description of fatigue

Among patients with cancer, fatigue is commonly referred to as cancer-related fatigue. Fatigue is a multifactorial condition marked by extreme tiredness and an inability to function because of lack of energy.³⁵⁷ According to National Comprehensive Cancer Network guidelines, ratings of fatigue of 4 or higher on a scale from 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 may 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.³⁵⁸⁻³⁶⁰ Fatigue has disruptive consequences and can have a negative impact on a patient’s QOL, mood, and self-esteem.¹⁹² 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.

C-graded and D-graded therapies for fatigue

There are no A-graded or B-graded therapies to report for fatigue. Trials evaluating hypnosis,^{97,98} ginseng,^{99,100} acetyl-L-carnitine,¹⁰⁷ and guarana^{108,109} have examined their effects on fatigue during treatment. Two trials from a single research group reported beneficial effects of hypnosis on fatigue during treatment; therefore, hypnosis can be considered for fatigue during treatment (grade C). Neither acetyl-L-carnitine nor guarana is recommended for improving fatigue during treatment because of a lack of effect in clinical trials among patients with cancer (grade D for both). Ginseng received a grade C for fatigue during treatment

based on a single, high-quality trial with a large sample size.⁹⁹ A previous large, high-quality, dose-finding study by the same group indicated that a higher dose was more effective.¹⁰⁰ In subset analyses in the subsequent trial, which tested the receipt of ginseng by patients who reported fatigue either during or after treatment, the results showed that ginseng was more effective in patients undergoing active treatment. Trials testing the effects of acupuncture^{51,101-103} and yoga^{45,80,84,104-106} for post-treatment fatigue yielded modest results (grade C). Four high-quality acupuncture trials assessed fatigue as the primary outcome; 3 of those 4 trials included a large sample size.^{51,101-103} Acupuncture for post-treatment fatigue received a grade of C mainly because of inconsistent comparison groups across the trials, including sham acupuncture,^{101,103} standard of care,^{51,102} self-administered acupuncture,¹⁰² and wait-list control.¹⁰³ Three trials evaluated yoga for post-treatment fatigue as a primary outcome^{45,80,106}; only one study had a large sample size⁸⁰ and the other 2 reported contrasting results.^{45,106}

Use of Integrative Therapies for QOL

Description of QOL

QOL is a multidimensional construct that typically measures the functioning of emotional, physical, role, and social domains using validated questionnaires.³⁶¹ The majority of patients with breast cancer report some level of diminished QOL during cancer treatment and/or survivorship.³⁶² 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 QOL.^{302,363-365} Decrements in QOL may persist upon the conclusion of treatment, during chronic/long-term hormonal and biotherapies, and into survivorship.³⁶⁶

Meditation (A grade)

Overview of meditation interventions for QOL. Meditation is recommended for improving QOL in patients with breast cancer (grade A). This recommendation is based on 7 RCTs, completed between 2009 and 2013, which used meditation for this indication (see Supporting Information Table 4).^{27-29,73-75,127} QOL was the primary outcome in 4

of those 7 trials.^{73-75,127} In 4 trials,^{27-29,74} a meditation intervention group was compared with a usual care or waitlist control condition group, and 3 other trials^{73,75,127} used a 3-arm design. Study participants included women undergoing radiation therapy for breast cancer, patients with newly diagnosed stage 0 through IV breast cancer, 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 interventions for anxiety/stress reduction and depression outcomes (see above).

Previous research has supported the role of MBSR interventions for improved QOL in heterogeneous samples of patients with cancer and survivors, with effect sizes ranging from small to large on QOL scales.^{319,367,368} One review in particular assessed the impact of MBSR on QOL in patients with breast cancer.¹⁷⁵ In that review, the authors identified only 3 studies that met their criteria and also measured QOL as an outcome.^{29,127,292} Of the 3 studies that measured QOL, only one (also included in our review) reported significant improvements after MBSR intervention²⁹ relative to results in control or comparator groups. The other 2 trials reported no significant improvements in QOL 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 QOL.³¹⁶ The analyses specific to the QOL outcome included 248 patients in 6 studies and reported a small effect size ($P < .01$). The authors suggest that, although these findings support the use of MBSR for improving QOL, more well conducted RCTs are required that implement adequate controls, longer follow-up periods, larger sample 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 QOL 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 MBIs³²¹ are cost-effective and beneficial therapies that can be used as adjuncts to traditional individual counseling or psychotherapy.

Future research in meditation interventions for QOL. To improve specificity of the effective components of meditation and to compare meditation interventions with other MBIs, research assessing meditation as a treatment for improved QOL and/or physical functioning should be extended to directly compare meditation with other forms of therapy, including individual counseling, cognitive

behavioral therapy, and other MBIs, similar to the therapies compared in the trial by Carlson et al.²⁶

Yoga (B grade)

Overview of yoga interventions for QOL. Yoga is recommended for improving QOL in patients with breast cancer (grade B). This recommendation is based on 12 RCTs, completed between 2006 and 2015, which tested a variety of yoga programs (see Supporting Information Table 4).^{43,46-48,82-85,104-106,128} QOL was the primary outcome for 6 of those 12 trials.^{47,82,83,105,106,128} In 10 trials, a yoga intervention group was compared with a usual care or waitlist control condition group, and 2 other trials used brief supportive therapy as a comparison group.^{43,85} Study participants included women undergoing radiation therapy or chemotherapy for breast cancer, patients with newly diagnosed breast cancer, 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). In total, 4 different types of yoga interventions were investigated, including: Iyengar or Hatha yoga,^{82-84,104-106} an integrated yoga program,^{43,85,128} pranayama or yoga breathing,^{46,47} and Patanjali's yoga sutras.⁴⁸

Another systematic review and meta-analysis assessed the impact of yoga interventions on QOL and psychological health specifically in patients with breast cancer and survivors.³³⁰ Overall, 12 RCTs were included in that 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 ($P < .01$). However, it is 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 QOL and is recommended for use in patients with breast cancer.

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

C-graded and D-graded therapies for QOL

Trials in acupuncture,^{49,51,102,129,130} mistletoe,¹³¹⁻¹³⁴ qigong,^{135,136} reflexology,¹³⁷⁻¹³⁹ and stress management^{36-38,95,96,140,141} have assessed the effect of these

therapies on QOL and received a grade of C, indicating that they can be considered for use. The 5 trials evaluating acupuncture had mixed findings and small sample sizes; future studies should replicate the trials of acupuncture that compared real versus sham acupuncture, which were the study designs that produced no effect.^{49,102} Two trials^{135,136} found that qigong had beneficial effects on QOL; however, those studies were fairly small and should be replicated in larger and more diverse patient populations. Three large, high-quality trials¹³⁷⁻¹³⁹ of reflexology for improving QOL reported mixed findings. The trials of stress management had conflicting results and used a broad range of control groups.^{36-38,95,96,140,141}

There is some evidence that mistletoe may improve QOL in patients with breast cancer.¹³¹⁻¹³⁴ However, although the trials have study quality and sample sizes that could merit a grade of B, the final decision to assign a grade of C is because of 2 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 nonspecificity and variability in formulations of the agents tested. Second, mistletoe is an injected bioactive compound with a potential for a differential risk/benefit ratio because of 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 MBIs, because they have lower risk profiles. The grade C recommendation is based on 4 RCTs, completed between 2004 and 2014, which tested the use of mistletoe for improving QOL.¹³¹⁻¹³⁴ QOL was the primary outcome in all 4 trials in which a mistletoe product group was compared with a placebo^{131,132} or standard care^{133,134} control group. The mistletoe products tested, all of which injected subcutaneously, included PS76A2,^{131,132} Helixor A,¹³⁴ and Iscador.¹³³ Study participants included women who were receiving chemotherapy 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 QOL in patients with breast cancer, double-blind trials need to directly evaluate and compare the different products available and also should 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^{178,369} of controlled clinical trials of mistletoe, including a Cochrane database analysis, did find an improvement in survival in the adjuvant setting. Although this outcome was outside the scope of this current review, the 2 reviews suggested a QOL benefit and called for further confirmatory trials.^{178,369}

Use of Integrative Therapies for CINV

Description of CINV

CINV is experienced by some patients with cancer after they receive chemotherapy.^{197,370,371} Acute CINV is typically defined as occurring during the first 24-hour period after chemotherapy administration. It is believed that delayed or late CINV is mediated by different mechanisms compared with acute CINV³⁷² and occurs more than 24 hours after chemotherapy administration. In a large, prospective study of patients with breast cancer who were receiving chemotherapy, 37% reported any nausea, and 13% reported any vomiting during the first 24-hour period.³⁷³ In the 2 to 5 days after chemotherapy administration, 70% reported any nausea, and 15% reported any vomiting.^{195,373} The 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 decreases 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 QOL.^{370,374-376} Standard of care antiemetics 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.^{197,371} Most contemporary studies use as the endpoint the proportion of patients achieving a complete response, defined as no emesis or use of rescue medication. In addition, antiemetics themselves have side effects, such as headaches, constipation, and neuropsychiatric effects, and thus merit study designs that replace medications with integrative approaches and use equivalence or nonsuperiority designs for the CINV and medication side-effect endpoints.

Acupressure (B grade)

Overview of acupressure interventions for CINV. For patients with breast cancer who are receiving chemotherapy, acupressure can be considered as an addition to antiemetics to help control nausea and vomiting (grade B). This recommendation is based on results from 3 RCTs, reported between 2000 and 2007, of an acupressure intervention used in conjunction with antiemetics to treat CINV (see Supporting Information Table 5).⁶¹⁻⁶³ Acute and delayed nausea and vomiting were the primary outcomes for all 3 trials. In 2 trials,^{61,63} the acupressure plus usual care intervention group was compared with a usual care group. The third trial⁶² was a 3-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 an attempt to control for the experience of receiving the treatment; if it is implemented well, participants will not be able to discern between the true and sham techniques.) Study participants included patients with breast cancer 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^{61,62} using a finger and wearing acupressure wristbands.⁶³ Across the 3 trials, acupressure therapy produced significant decreases in nausea, retching, and vomiting ($P < .05$ for multiple outcomes assessing CINV) (for details, see Supporting Information Table 5).

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.³⁷⁷ Other studies of acupressure to reduce nausea and vomiting have shown efficacy in other populations, including pregnant women and postoperative patients, including after thyroidectomy.³⁷⁸ All of these studies were conducted with acupressure wristbands placed on both the patient's arms at the PC6 acupoint.³⁷⁹ A review of acupuncture and acupressure for CINV control among patients with breast cancer concluded that the therapies are both safe and effective.³⁸⁰ A secondary data analysis of the multicenter study by Dibble et al⁶² concluded that patients with breast cancer 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.³⁸¹ However, a recent publication by Molassiotis, a lead author of one of the included trials in our review, and colleagues³⁸² 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 patients with breast cancer.

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 who 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 patients with breast cancer during chemotherapy (grade B). This recommendation is based on 2 RCTs, published in 2000 and 2012 (see Supporting Information Table 5),^{64,65} as well as the 1997 National Institutes of Health Consensus Conference on acupuncture.³⁸³ However, most of those trials predated the use of newer agents, including, 5-hydroxytryptamine type 3 (5-HT₃) and neurokinin-1 (NK1) receptor antagonists, which have become standard antiemetic therapies for patients who receive highly emetogenic chemotherapy. We do not have a body of evidence to evaluate whether the addition of acupuncture to contemporary antiemetics yields added benefit. Participants in the trials in this analysis included patients with breast cancer who had received moderately high or highly emetogenic chemotherapy without a 5-HT₃ or NK1 receptor antagonist.¹⁹⁷ Both trials used PC6 and ST36 acupoints and sham controls, and both trials evaluated the effects of these acupoints on acute and delayed CINV. One trial also used acupoint LI4 and found that electroacupuncture was no better than sham electroacupuncture and that a likely contributor to the lack of effect of electroacupuncture in CINV was the that the study evaluated only feasibility with a minimal electroacupuncture intervention and without a no-acupuncture arm.⁶⁴ The second trial indicated that the patients receiving electroacupuncture experienced significantly fewer emesis episodes over the 5 days of the acupuncture intervention than the patients receiving mock therapy or antiemetics alone ($P < .001$).⁶⁵ 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 ($P = .01$).

A multicenter study by Yang et al³⁸⁴ that compared ST36 electroacupuncture plus antiemetics with antiemetics alone in 246 patients with heterogeneous cancers indicated an additive effect with the use of electroacupuncture ($P < .01$), with greater decreases in nausea and vomiting scores ($P < .001$) compared with the use of antiemetics alone. Two early studies by Dundee and colleagues^{385,386} reported significantly less CINV with a PC6 electroacupuncture intervention, although the investigators noted that the brevity of emetic action was a major problem. In a recent review of acupuncture studies, including those that evaluated CINV, investigators concluded that only the electroacupuncture study by Shen et al⁶⁵ had a low risk of bias.¹⁶⁰ In addition, an earlier meta-analysis by Ezzo et al³⁸⁷ determined that electroacupuncture, but 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.^{119,388-392} In addition to possibly reducing CINV, PC6 stimulation has been associated with other positive benefits, including analgesic,¹¹⁹ sedative,³⁹³ and anxiolytic effects.³⁹⁴ Furthermore, 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 by Yang et al,³⁸⁴ 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.¹⁶⁰

Future research in electroacupuncture interventions for CINV. Future trials on the use of electroacupuncture interventions for CINV in patients with breast cancer can focus on 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 patients with cancer, and this modality could be tested and compared with less potent antiemetics or best supportive care when other therapies are ineffective.

C-graded and D-graded therapies for CINV

Three trials of ginger⁶⁶⁻⁶⁸ and 2 trials of relaxation^{59,69} have examined their effects on CINV as a primary outcome. Although the number of trials was limited, the results suggested enough of an effect to result in a grade C recommendation 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 because of a lack of effect from 2 trials^{70,71} in which CINV was assessed as a secondary outcome (grade D).

Use of Integrative Therapies for Acute Radiation Dermatitis

Because 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 patients with breast cancer is acute skin irritation. Late changes to normal tissue can occur years after therapy and can include soft tissue fibrosis, lymphedema, lung, and heart and chest wall damage.³⁹⁵ 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 several weeks after treatment.³⁹⁵ 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.³⁹⁶ The Cooperative Group Common Toxicity Criteria (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 indicating erythema and grade 4 indicating ulceration. Most patients with breast cancer develop mild-to-moderate acute skin reactions of grade 1 through 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.³⁹⁶

D-graded therapies for acute radiation dermatitis

There are no therapies graded A, B, or C to report for acute radiation dermatitis after treatment. Aloe vera gel and hyaluronic cream are not recommended as a standard therapy to prevent or treat acute radiation dermatitis simply because of lack of effect (grade D). Our review consisted of 2 quality studies for each product with large sample sizes for both the aloe vera^{22,23} and hyaluronic cream^{24,25} trials. 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 patients with breast cancer and include hot flashes, intense sweating, and flushing on the face and chest, and they may come with heart palpitations and anxiety.³⁹⁷ These symptoms occur episodically, including nocturnally, when night sweats can significantly disrupt women's sleep. According to the 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.³⁹⁸ While vasomotor symptoms may resolve on their own, 20% of affected women suffer from persistent hot flashes 4 years after their last menses.³⁹⁷ Together, vasomotor symptoms can significantly impact women's QOL.³⁹⁸

C-graded and D-graded therapies for vasomotor outcomes

There are no A-graded or B-graded therapies to recommend for vasomotor outcomes. Acupuncture can be considered as a therapy for hot flashes based on 9 trials that assessed acupuncture for hot flashes (grade C).^{49,91,92,143-148} Seven of those trials assessed hot flashes as the primary outcome,^{91,92,143-146,148} and only one trial¹⁴⁸ had more than

100 participants. Overall, the literature showed mixed findings; however, the single, large trial demonstrated significant reductions in hot flashes in their electroacupuncture group compared with sham and control groups. The use of soy as a therapy for hot flashes is not recommended because of lack of effect (grade D). Three large trials¹⁴⁹⁻¹⁵¹ 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 after treatment, such as surgery or radiation therapy, in which 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.¹⁶⁶ 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 patients with breast cancer and survivors, lymphedema is most common in the upper extremities and sometimes in the breast and/or chest wall, and it can occur up to 30 years after treatment. Because of differences in diagnosis, characteristics of the patients studied, and inadequate follow-up, the overall incidence of arm lymphedema after breast cancer reportedly ranges from 8% to 56%.³⁹⁹ Breast cancer survivors with arm lymphedema in particular have been found to have decreased QOL and increased psychological distress and disability compared with survivors without lymphedema.³⁹⁹⁻⁴⁰¹

C-graded therapies for lymphedema

There are no A-graded or B-graded therapies to report for lymphedema. Two trials assessed low-level laser therapy,^{110,111} and 7 trials assessed manual lymphatic drainage¹¹²⁻¹¹⁸ for the treatment of lymphedema as a primary outcome. The 2 trials that evaluated low-level laser therapy were small in sample size and showed mixed findings. Only 2 of the 7 trials that assessed manual lymphatic drainage had a sample size greater than 100 participants.^{113,118} Overall, the literature suggests that manual lymphatic drainage and compression bandaging are equivalent.¹¹⁴⁻¹¹⁶ 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 CIPN

CIPN

Cancer treatments, including chemotherapy, may cause damage to the peripheral nerves, resulting

in neuropathy.⁴⁰² The CGCTC categorizes neuropathy under neurologic-sensory and grades it from 0 to 3, with 3 indicating 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, and swallowing or breathing difficulties. Autonomic nerve damage can cause dizziness or faintness and digestive, sexual, sweating, and urination problems.⁴⁰²

H-graded therapies for CIPN

There are no A-graded 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 because of harm (grade H). A single, large, high-quality study¹⁰⁷ assessing the use of acetyl-L-carnitine capsules to prevent CIPN after taxane therapy as a primary outcome 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.”⁴⁰³ 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.⁴⁰⁴ Pain is commonly experienced by patients who have breast cancer with a prevalence ranging from 40% to 89%.⁴⁰³ Pain management requires proper assessment, including measurement of intensity.⁴⁰⁴ It is also important to evaluate the impact of pain on the patient’s physical, mental, and social health, because pain can negatively impact their functional status and QOL. Pain management can include both pharmacologic and nonpharmacologic modalities. Proper education about treatment and longitudinal follow-up are essential.

C-graded therapies for pain

There are no A-graded or B-graded therapies to report for pain. Healing touch⁹³ for pain after chemotherapy; music therapy,^{31,34} hypnosis,^{125,126} and acupuncture¹¹⁹ for pain after surgery; and acupuncture¹²⁰⁻¹²⁴ for pain related to aromatase inhibitor-associated musculoskeletal symptoms were examined, and each received a grade of C, indicating that they can be considered as a therapy for pain. A single, large trial assessed healing touch⁹³ for pain after chemotherapy as

a secondary outcome and demonstrated small positive effects favoring the therapy. Similarly, trials that assessed music therapy,^{31,34} hypnosis,^{125,126} and acupuncture¹¹⁹ for pain after surgery as a primary outcome demonstrated small positive effects favoring the therapy. However, there is a lack of multiple, large trials to support each therapy. Finally, 5 trials evaluated acupuncture for pain related to aromatase inhibitor-associated musculoskeletal symptoms as the primary outcome.¹²⁰⁻¹²⁴ All of those trials had small sample sizes and reported mixed findings.

Use of Integrative Therapies for Sleep Disturbance

Sleep disturbances

Studies have shown that nearly one-half of all patients with breast cancer have sleep-related problems from a range of causes, including side effects of antineoplastic medications, long hospital stays, or stress.^{405,406} In addition, growing numbers of patients with breast cancer are obese,⁴⁰⁷ 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 patients with cancer and often occurs along with anxiety and depression.⁴⁰⁸ The CTCAE measures insomnia under psychiatric disorders from grade 1 through grade 3, with grade 3 indicating severe difficulty falling asleep, staying asleep, or waking up early.

C-graded therapies for sleep disturbance

There are no A-graded 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^{45,48,79,84,172}; and, in 4 of those trials, sleep was a secondary outcome. Two trials were of high quality, with more than 100 participants.^{79,142} Overall, the body of literature showed no greater effect on sleep quality for health education classes, stretching groups, and wait-list controls.

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 patients with breast cancer, including anxiety, stress, depression, and mood disturbances. In addition, it has been demonstrated that meditation improves QOL and physical functioning; yoga improves QOL and fatigue; massage improves mood; and acupressure and electroacupuncture decrease CINV. Given the high level of evidence of benefit

coupled with the relatively low level of risk, these therapies can be incorporated as an option into patient care, 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 a 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, although 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 numbers of integrative modalities with grades of A or B emphasize the need for all cancer care providers to initiate a dialogue early in their relationship with 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 is 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 that includes reviews of integrative therapy for patients with breast cancer and other cancer populations. For example, numerous reviews support the use of integrative therapies, including passive music therapy,³²² stress-management programs,³²⁴ various yoga practices,³²⁹ meditation and MBSR,³¹⁵ massage,³⁴⁹ and relaxation techniques,³³⁷ 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 populations of patients with cancer.³⁷⁷ There are mixed findings in the areas of meditation and MBSR for QOL^{175,316} and electroacupuncture for CINV,¹⁶⁰ 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 participants in the clinical trials we 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 premenopausal versus postmenopausal 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

Patients with cancer face several psychological and physical challenges as they move through cancer diagnosis, treatment, and survivorship. According to National Comprehensive Cancer Network 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.^{194,409}

On the basis of recent estimates from the US National Health Interview Survey, 75% of individuals with a history of cancer use one or more complementary and integrative therapies.⁴¹⁰ Many North American cancer centers now operate formal integrative oncology programs. Because 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 are provided free of charge to patients, some are entirely paid for out-of-pocket by patients, and some are a combination of both. Often, mind-body therapies already are available from trained clinical staff 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 requires not only funding and infrastructure but also 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. Although 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-based 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.^{411,412}

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 multimodal therapies 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 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 conventional therapies. In this review, when possible, the NCI 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 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 US Food and Drug Administration is increasingly using CTCAE patient-reported outcomes (CTCAE-PROs) to monitor treatment side effects.^{413,414} Ideally, trials will include systematic evaluation of both provider (ie, CTCAE) and patient (ie, 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 participants to most of the integrative modalities studied, because most measures are subjective and thus are susceptible to suggestive biases in which patients perceive benefit to an intervention simply because they are receiving it. By 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. In addition, the use of both subjective and objective patient-reported outcomes should be used within a mixed-methods model. This approach can be used in both clinical trials and in prospective observational studies. To better enable real clinical uptake and change, knowledge translation experts, patients with cancer, 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 for patients with breast cancer who require supportive care. Billions of dollars are spent each year on complementary and integrative health therapies with unknown benefits and on those that have thus far been shown to be ineffective.⁴¹⁰ Research in this area could save large amounts of health care 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 on patient needs in their specific setting and context. ■

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