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Clinical Practice Guidelines on the Use of Integrative Therapies as Supportive Care in Patients Treated for Breast Cancer

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Background The majority of breast cancer patients use complementary and/or integrative therapies during and beyond cancer treatment to manage symptoms, prevent toxicities, and improve quality of life. Practice guidelines are needed to inform clinicians and patients about safe and effective therapies.

Methods Following the Institute of Medicine's guideline development process, a systematic review identified randomized controlled trials testing the use of integrative therapies for supportive care in patients receiving breast cancer treatment. Trials were included if the majority of participants had breast cancer and/or breast cancer patient results were reported separately, and outcomes were clinically relevant. Recommendations were organized by outcome and graded based upon a modified version of the US Preventive Services Task Force grading system.

Results The search (January 1, 1990–December 31, 2013) identified 4900 articles, of which 203 were eligible for analysis. Meditation, yoga, and relaxation with imagery are recommended for routine use for common conditions, including anxiety and mood disorders (Grade A). Stress management, yoga, massage, music therapy, energy conservation, and meditation are recommended for stress reduction, anxiety, depression, fatigue, and quality of life (Grade B). Many interventions ($n = 32$) had weaker evidence of benefit (Grade C). Some interventions ($n = 7$) were deemed unlikely to provide any benefit (Grade D). Notably, only one intervention, acetyl-L-carnitine for the prevention of taxane-induced neuropathy, was identified as likely harmful (Grade H) as it was found to increase neuropathy. The majority of intervention/modality combinations ($n = 138$) did not have sufficient evidence to form specific recommendations (Grade I).

Conclusions Specific integrative therapies can be recommended as evidence-based supportive care options during breast cancer treatment. Most integrative therapies require further investigation via well-designed controlled trials with meaningful outcomes.

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Rationale and Importance

Worldwide, an estimated 33%–47% of individuals diagnosed with cancer use complementary, alternative, or integrative therapies during cancer treatment (1). Women with breast cancer are among the highest users of such therapies and usage has been increasing (2–7). An estimated 48%–80% of North American breast cancer survivors use complementary and integrative therapies following diagnosis (2,4,5,8–12). Clear clinical practice guidelines are needed to inform clinicians and patients about the evidence supporting or discouraging the use of specific complementary and integrative therapies for defined outcomes during and beyond breast cancer treatment, including symptom management.

Definitions

Complementary and alternative therapies are generally defined as any medical system, practice, or product that is not part of conventional medical care (13,14). Examples include natural products (ie, vitamins, minerals, botanicals, and fish oil) and mind–body practices (ie, yoga, meditation, acupuncture, and massage). *Complementary medicine* is the use of a therapy in conjunction with conventional medicine (14). *Alternative medicine* is the use of a therapy in place of conventional medicine. *Integrative medicine* is the use of evidence-based complementary practices in coordination with evidence-based conventional care. *Integrative oncology* refers to the use of complementary and integrative therapies in collaboration with conventional oncology care.

The Society for Integrative Oncology

In 2004, the Society for Integrative Oncology (SIO) (http://www.integrativeonc.org/) was established by leaders of integrative oncology research and practice at major cancer centers in the United States, and has since expanded to include members from more than 29 countries. The mission of SIO is to advance evidence-based, comprehensive, integrative health care to improve the lives of

people affected by cancer. SIO supports the research and evidence-based use of complementary and integrative medicine therapies in cancer patients. In 2007, SIO published general practice guidelines on the use of integrative therapies across all populations of cancer patients and survivors, which were updated in 2009 (15). SIO was invited by the American College of Chest Physicians to develop guidelines on the use of integrative therapies by lung cancer patients, which were published in 2007 (16) and updated in 2013 (17). SIO guidelines are posted on national clinical guidelines websites (http://nccam.nih.gov/; http://www.guideline.gov/).

In 2013, SIO recognized the need to further develop clear, usable, methodologically strong, and transparent guidelines on the use of integrative therapies for patients with specific types of cancer. Given that breast cancer patients are among the highest users of complementary and integrative medicine, and that the majority of relevant research to date has been conducted among this population, we focus this set of guidelines on complementary and integrative medicine use during or following breast cancer treatment as supportive care for the prevention and amelioration of symptoms, side effects, and treatment toxicities. SIO plans to update these specific guidelines every 3 years and to develop additional guidelines for other disease sites.

Purpose

These guidelines are designed to inform clinicians, patients, and researchers of the state-of-the-science regarding the evidence-based use of complementary and integrative therapies for patients receiving breast cancer treatment. The American Society of Clinical Oncology recently published clinical guidelines on the management of specific symptoms, including fatigue (18), anxiety/depressive symptoms (19), and chemotherapy-induced peripheral neuropathy (20). The SIO guidelines differ in that they provide a single comprehensive document evaluating the evidence on a wide variety of integrative therapies used to address defined symptom complexes associated with conventional oncology treatment, including chemotherapy, radiation, and surgery, and include integrative therapies not considered in the American Society of Clinical Oncology guidelines. Following methods outlined by the Institute of Medicine (21), the guidelines were developed based upon a systematic review of the published literature on randomized controlled trials investigating the use of complementary and integrative medicine during breast cancer treatment for supportive care.

Methods

Selection of Expert Panel

A multidisciplinary panel of experts in oncology and integrative medicine was assembled to prepare these clinical practice guidelines. Panel members have expertise in medical oncology, radiation oncology, nursing, psychology, naturopathic medicine, traditional Chinese medicine, acupuncture, epidemiology, biostatistics, and patient advocacy.

Conflict of Interest

Financial conflicts of interest, including research support, were reviewed for all authors. There are no financial conflicts of interest to disclose. We note that some authors have conducted/authored some of the studies included in the review.

Rationale for Selected Interventions

A summary of the integrative modalities and clinical outcomes of interest identified and assessed by the expert panel are shown in Table 1. Several interventions were excluded for the following reasons. Some have already been well summarized by other groups [eg, diet (22,23), physical activity (22–24)], while others already have a large evidence-base and are often no longer included in the definition of integrative or complementary interventions as they have become mainstream [eg, cognitive-behavioral therapy (25), psychoeducation (26), counseling (27), and support groups (26)]. Others were in early or pilot stages of research (eg, attention restoration therapy) or were not considered integrative interventions for the purposes of these guidelines (eg, prayer, spirituality).

Rationale for Selected Outcomes

Currently, available integrative medicine guidelines focus on and are organized around individual therapies. Guidelines organized around symptoms are more practical and useful to clinicians. Only outcomes considered to be clinically relevant to patients were selected, including quality of life, organ toxicities, measurable symptoms, adverse events, and laboratory values linked to health outcomes (ie, blood count alterations leading to clinical consequences). We acknowledge that these patient-centered outcomes are largely based upon the conventional medical paradigm; other systems of medicine may value other patient-centered outcomes, which are not included here due to a lack of randomized controlled trials on such outcomes. Tumor response, recurrence, and survival outcomes were not addressed in these guidelines due the paucity of quality trials in this area. Biomarkers not firmly linked to clinical outcomes, such as immune parameters, were excluded.

Methodology for Search

We performed a systematic review of published randomized controlled trials assessing the safety and effectiveness of integrative modalities as supportive care in women receiving standard breast cancer treatment. The panel of experts compiled search keywords associated with the interventions and outcomes of interest (see Supplementary Appendix 1, available online). Nine databases (EMBASE, MEDLINE, PubMed, CINAHL, PsychINFO, Web of Science, SCOPUS, AMED, and Acutrial) were searched for studies published between January 1, 1990 and December 31, 2013. This search yielded 4900 unique articles. Article titles and abstracts were initially screened by at least two reviewers for inclusion for full review. Articles were selected for inclusion in the systematic review if they met the following criteria: 1) randomized controlled trial; 2) available in English; 3) included at least 50% breast cancer patients and/or reported results separately for breast cancer patients; 4) used an integrative modality as an intervention during standard treatment with surgery, chemotherapy, radiation therapy, and/or hormonal therapy, or addressed long-term side effects resulting from diagnosis and/or treatment; and 5) had an outcome of interest as defined in Table 2 (28). We excluded other systematic reviews and meta-analyses. Full-text of all articles that met these criteria were assembled in an online database accessible to the working group (Mendeley database, www.mendeley.com).

Table 1. Summary of systematic review of randomized controlled trials on the use of integrative therapies during breast cancer treatment*

Clinical population	BC patients during treatment, including surgery, CT, hormonal/biological therapy, and RT
Clinical question	What integrative therapies can be used to prevent, treat, and manage symptoms and side effects encountered during breast cancer treatment?

Clinical applications	Recommendations	Strength of evidence
Anxiety/stress reduction	Music therapy is recommended for reducing anxiety during RT and CT sessions	B
	Meditation is recommended for reducing anxiety in BC patients and those undergoing RT	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	B
	Yoga is recommended for reducing anxiety in BC patients undergoing RT +/– CT and suggested for fatigued patients	B
	Acupuncture can be considered for reducing anxiety in fatigued BC patients	C
	Massage can be considered for short-term reduction of anxiety in BC patients	C
	Relaxation can be considered for treating anxiety during treatment	C
Depression/mood	Meditation, particularly MBSR, is recommended for treating mood disturbance and depressive symptoms in BC patients undergoing RT	A
	Relaxation is recommended for improving mood and depressive symptoms when added to SC	A
	Yoga is recommended for improving mood in women undergoing RT +/– CT and for fatigued BC patients in addition to SC	A
	Massage is recommended for improving mood disturbance in posttreatment BC patients	B
	Music therapy is recommended for improving mood in newly diagnosed BC patients	B
	Acupuncture can be considered for improving mood in postmenopausal women experiencing hot flashes or fatigue	C
	Healing touch can be considered for improving mood in BC patients undergoing CT	C
	Stress management interventions with or without exercise can be considered for improving mood in BC patients	C
Fatigue	Energy conservation counseling is recommended for the treatment of fatigue	B
	American ginseng can be considered as an herbal approach for the treatment of fatigue in BC patients	C
	Acupuncture can be considered for the treatment of fatigue after the completion of cancer treatments	C
	Modified qigong can be considered for the treatment of fatigue in BC patients	C
	Acetyl-L-carnitine is not recommended for the treatment of fatigue due to lack of effect	D
	Guarana is not recommended as an herbal for the treatment of fatigue due to lack of effect	D
Sleep	Stress management techniques can be considered for the treatment of sleep disruption	C
	Gentle yoga can be considered for the treatment of sleep disruption	C
Quality of life and physical functioning	Meditation is recommended for improving quality of life among BC patients	A
	Acupuncture can be considered for improving quality of life among cancer patients	C
	Guided imagery can be considered for improving quality of life among BC patients	C
	Mistletoe can be considered for improving quality of life among BC patients	C
	Qigong can be considered for improving quality of life in cancer patients	C
	Reflexology can be considered for improving quality of life among BC patients	C
	Stress management can be considered for improving quality of life among BC patients	C
	Yoga can be considered for improving quality of life among BC patients	C
	Exercise/awareness can be considered for improving functioning among BC patients	C
	Energy conservation is not recommended for improving functioning among BC cancer patients due to lack of effect	D
CINV	Acupressure can be considered for BC patients receiving CT as an addition to antiemetics to help control nausea and vomiting during CT	B
	Electroacupuncture can be considered for BC patients as an addition to antiemetics to control vomiting during CT	B
	Ginger can be considered for BC patients receiving CT, without concurrent RT as an addition to antiemetics for the control of acute nausea	C
	PMR can be considered for BC patients receiving CT as an addition to antiemetics to help control nausea and vomiting during CT	C
	Glutamine is not recommended for use by BC patients receiving CT for the treatment of CINV due to lack of effect	D

(*Table continues*)

Table 1. Continued

Clinical applications	Recommendations	Strength of evidence
Pain	EASE can be considered for pain associated with CT among unemployed individuals	C
	Massage and healing touch can be considered for pain associated with CT	C
	Music therapy can be considered to relieve pain associated with surgery	C
	A physical training program that includes a mind–body modality can be considered for relieving pain associated with surgery among BC patients	C
	Hypnosis can be considered for relief of associated with surgery in BC patients	C
	Acupuncture can be considered as a nonpharmacologic approach to the short-term treatment of AIMSS	C
	Electroacupuncture can be considered as a nonpharmacologic approach to the short-term treatment of AIMSS	C
Neuropathy	Acetyl-L-carnitine is not recommended for prevention of neuropathy in BC patients due to harm	H
Lymphedema	Laser therapy can be considered as a treatment for lymphedema in BC patients	C
	MLD and compression bandaging have been shown to be equivalent. MLD can be considered for treatment of lymphedema in BC patients who have sensitivity to bandaging	C
Hot flashes	Acupuncture can be considered for decreasing the number of hot flashes in BC patients	C
	Electroacupuncture can be considered for decreasing the number of hot flashes in BC patients	C
	Soy is not recommended for the treatment of hot flashes in BC patients due to lack of effect	D
Acute radiation skin reaction	Aloe vera is not recommended as a standard therapy to prevent or treat acute radiation skin reaction due to lack of effect	D
	Hyaluronic acid cream is not recommended as a standard therapy to prevent or treat acute radiation skin reaction due to lack of effect	D

* AIMSS = aromatase inhibitor-associated musculoskeletal symptoms; BC = breast cancer; CINV = chemotherapy-induced nausea vomiting; CT = chemotherapy; EASE = energy and sleep enhancement; MBSR = mindfulness-based stress reduction; MLD = manual lymphatic drainage; PMR = progressive muscle relaxation; RT = radiation therapy; SC = standard care.

Table 2. List of interventions and clinical outcomes of interest

Intervention
Acupuncture
Creative therapies
Hypnosis
Imagery/relaxation
Meditation
Mind-body practices
Natural products (eg, botanicals, vitamins, minerals)
Stress management
Tai Chi/qigong
Yoga
Whole systems*
Clinical outcomes of interest (in alphabetical order)
Fatigue**
Gastrointestinal**
Gynecological
Hematological
Lymphedema**
Neurological**
Neuromuscular**
Pain**
Psychological**
Quality of life**
Renal
Skin**
Sleep**
Vasomotor symptoms**

* Whole systems are defined as an approach to health care in which practitioners apply bodies of knowledge and associated practices to maximize the patients' capacity to achieve mental and physical balance and restore their own health, using individualized, nonreductionist approaches to diagnosis and treatment. In whole systems, the practitioner–patient relationship plays an important role and continues to evolve over time (28).

** Indicates where Grades A, B, C, D, and H recommendations are made in these guidelines, based upon quality of evidence.

A second round of screening consisted of a full-text scan to further remove articles that did not meet the inclusion criteria. A total of 203 articles met the criteria for final inclusion in the review.

Quality Scoring Criteria

Data from the 203 articles were extracted and scored based on study quality. Two reviewers were assigned each article and discrepancies were addressed by a third reviewer. Quality was assessed using the Jadad scoring scale (29) and a modified scale adapted from the Delphi scoring scale (30). See Supplementary Appendix 2 (available online) for a description of the quality scoring process and Supplementary Table 1 (available online) for a description of the quality scoring criteria. Study quality was not an exclusion criterion, but was a measure of validity, which along with the magnitude and certainty of benefit or harm, guided the grading of clinical recommendations.

Clinical Recommendations

For each modality applied to a specific outcome, a modified version of the US Preventive Services Task Force grading system was used to develop and grade recommendations (Tables 3 and 4) (31). If a trial had multiple outcomes, each outcome was assessed individually as it applied to the body of evidence for the specific modality/outcome pair. Ingestible and injectable natural products were specifically assessed for potential risk of toxicities and/or interactions with concurrent breast cancer therapies given the potential for drug interactions. The panel of experts compiled the data and drafted the recommendations. Draft guidelines were internally and externally reviewed by clinicians, researchers, patient advocates, and other stakeholders. Feedback was incorporated into the final guidelines.

Table 3. Society for integrative oncology grade of recommendations*

Grade	Definition	Suggestions for practice
A	Recommends the modality. There is high certainty that the net benefit is substantial.	Offer/provide this modality
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
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
D	Recommends against the service. There is moderate or high certainty that the modality has no net benefit.	Discourage the use of this modality
H	Recommends against the service. There is moderate or high certainty that the harms outweigh the benefits.	Discourage the use of this modality
I statement	Concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

* Adapted from US Preventive Services Task Force (31).

Clinical Guidelines

Overview. The recommendations from our systematic review are based on the strength of evidence using accepted standards. Along with trial quality and size, we considered the magnitude and type of benefit as well as harms to formulate practical, responsible, and defensible guidelines. Most of the guidelines are focused on the period during active cancer treatment and the period following when treatment side effects may persist. Cancer treatments include surgery, chemotherapy, radiation therapy, and hormonal therapy. The guidelines address both short- and long-term side effects (generally months or even years following treatment) and treatment toxicities that affect breast cancer survivors. These graded recommendations are intended to help clinicians and patients engage in informed and meaningful dialogue with each other regardless of their final course of action.

There are several key caveats to the recommendations presented herein. First, clinicians and patients should adopt shared decision-making approaches when assessing the risk-benefit ratio for each therapy. It is important to personalize the recommendations based upon patients' values and clinical characteristics (32). Specific considerations that can affect the recommendation of complementary and integrative therapies include, but are not limited to: stage of disease, the overall goal of anticancer therapy (ie, curative vs palliative); whether complementary and integrative therapies are given concurrently with anticancer therapy and if there is potential for interactions; known toxicity of specific anticancer therapy; patient performance status and patient adherence. Second, integrative approaches by definition are used alongside/in combination with conventional medical care and should be fully communicated to all health-care providers involved in the patient's care. All modalities should be administered by qualified and experienced providers, if applicable, who have the appropriate training, licensure, and credentialing. Ongoing communication and exchange of treatment summaries among all health-care providers should take place. Third, as is the case with most therapies, responses to integrative treatments are highly variable. Patients should be monitored for efficacy and toxicity, including futility and adverse effects, and encouraged to keep symptom logs and/or use validated patient-reported outcome tools (33–34). Treatment should be stopped for unfavorable or neutral risk/benefit effects. Most of the studies testing these therapies compared the intervention of interest to standard care, so we cannot make claims about comparative efficacy (ie, whether one intervention is better than another). Finally, patient preference, as well as cost, degree of invasiveness, and effort involved should be taken into account when considering treatment plans.

Of note, there were a large number of therapies that were deemed to have insufficient evidence to form recommendations. Supplementary Tables 2-13, available online, include references and information regarding such therapies. A small number of natural products that were investigated in large and/or multiple trials and did not have an effect were given a Grade D.

Anxiety and Stress

Music therapy [Grade B (35–39)] is recommended for the short-term relief of anxiety during radiation therapy and chemotherapy. Meditation [Grade B (40–43)] including mindfulness-based stress reduction, yoga [Grade B (44–51)], and stress management programs [Grade B (52–56)] are recommended to reduce longer term anxiety both during and after treatment. Longer stress management groups (55) are likely more effective than short home study programs (52). Acupuncture [Grade C (57)] can be considered for treating anxiety concurrent with ongoing fatigue. Relaxation [Grade C (58–62)] and massage therapy [Grade C (63–66)] both can be considered for the short-term relief of anxiety during treatment. In this section, outcomes of "pure" anxiety and stress were considered [eg, State-Trait Anxiety Inventory (67) and Perceived Stress Scale (68)]. Mixed

Table 4. Society for integrative oncology level of certainty of recommendations*

Level of certainty**	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative breast cancer patient populations. These studies assess the effects of the modality and conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the modality on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine breast oncology practice; and lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: the limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings that are not generalizable to routine breast oncology practice; and a lack of information on important health outcomes. More information may allow an estimation of effects on health outcomes.

* Adapted from US Preventive Services Task Force (31).

** Certainty is defined as "likelihood that the Society for Integrative Oncology Guidelines Working Group assessment of the net benefit of a supportive care service is correct." The net benefit is defined as benefit minus harm of the supportive care service as implemented in a general breast oncology population. The Society for Integrative Oncology Guidelines Working Group assigns a certainty level on the basis of the nature of the overall evidence available to assess the net benefit of a supportive care service.

measures of general mood [eg, Profile of Mood States (69)] were grouped in the next section with traditional depression outcomes [eg, Beck Depression Inventory (70)]. For the purposes of these guidelines, mindfulness-based stress reduction is considered to be a form of meditation. The primary emphasis of mindfulness-based stress reduction is on daily training in traditional contemplative mindfulness meditation practices including sitting, lying, and walking meditation with mindful movement using gentle Hatha yoga poses. For further details, see Supplementary Table 2, available online.

Depression and Mood

Meditation [Grade A (39,40–43,56,71)] particularly mindfulness-based stress reduction, is recommended for improving mood and depression during radiation therapy and posttreatment. Yoga alone [Grade A (44–49,51,75–78)] and relaxation [Grade A (58,60,61,79,80)] are also recommended for improving mood and depressive symptoms during radiation therapy and chemotherapy and in the presence of fatigue. For newly diagnosed patients, music therapy [Grade B (37,81,82)] is recommended to improve mood and depressive symptoms. Massage [Grade B (64–66,83–85)] is recommended for improving mood disturbance in posttreatment survivors. Stress management [Grade C (52–54)] can be considered to improve mood and depressive symptoms. Healing touch [Grade C (86,87)] can be considered for improving mood in patients undergoing chemotherapy. Acupuncture [Grade C (57,88)] can be considered for improving depressive symptoms in women suffering from hot flashes. For further details, see Supplementary Table 3, available online.

Fatigue

Energy conservation/activity management [Grade B (89)] is recommended for fatigue management. Qigong [Grade C (90,91)] and posttreatment acupuncture [Grade C (57,92–94)] can also be considered to manage fatigue. About 2000 mg daily of encapsulated American ginseng root powder standardized to 3% ginsenosides [Grade C (95,96)] can be considered to improve fatigue during chemotherapy and radiation. An estrogenic effect from a ginseng methanolic extract has been observed in breast cancer cell lines (97–100). However, the formulation studied in the trials was a whole root product for which no long-term evidence exists regarding safety or harm. Acetyl-L-carnitine [Grade D (101)] and guarana [Grade D (102,103)] are not recommended for the treatment of fatigue due to lack of effect. For further details, see Supplementary Table 4, available online.

Sleep Quality

Gentle yoga [Grade C (45,46,76,104)] and stress management techniques [Grade C (53,105)] can be considered for treatment of sleep disruption. For further details, see Supplementary Table 5, available online.

Global Quality of Life and Physical Functioning

Meditation [Grade A (40–42,72–74,106)] is recommended for improving quality of life, while relaxation and guided imagery [Grade C (79–81,107)], qigong [Grade C (90,108)], reflexology [Grade C (109–111)], stress management [Grade C (52,53,54,114)], and yoga [Grade C (46–49,75–78,115,116)] can also be considered. Acupuncture studies [Grade C (57,117,118)] demonstrated mixed results for improving quality of life, although no studies showed deleterious effect. Mistletoe [Grade C (119–121)] can be considered for improving quality of life in the short term, but there are limited data assessing long-term effects, interactions, and toxicities. There is some evidence of reversible hepatotoxicity at high doses of mistletoe (122,123). Exercise programs that include a relaxation/stress management component [Grade C (54,124)] can be considered as options for improving physical functioning, while programs oriented towards energy conservation [Grade D (89,125)] are not recommended. For further details, see Supplementary Table 6, available online.

Chemotherapy-Induced Nausea and Vomiting

Electroacupuncture [Grade B (126,127)], acupressure [Grade B (128–130)], and progressive muscle relaxation [Grade C (60,80)] can be considered as an addition to antiemetics for controlling chemotherapy-induced nausea and vomiting (CINV). There is stronger evidence on the use of acupuncture/electroacupuncture for CINV in other cancer populations (131–134). Ginger [Grade C (135,136)] in combination with antiemetics can be considered to control acute nausea, but not acute vomiting nor delayed nausea and vomiting. There is similar evidence on the use of ginger to control nausea in other populations (137,138). However, ginger should not be coadministered with the antiemetic aprepitant because of a

possible negative interaction between the two agents on delayed CINV (139). Glutamine [Grade D (140,141)] is not recommended for treatment of CINV due to lack of effect. For further details, see Supplementary Table 7, available online.

Pain

Healing touch [Grade C (87)] and energy and sleep enhancement programs [Grade C (125)] can be considered for treating pain during chemotherapy. Music therapy [Grade C (35,142)], a physical training program that includes a mind–body modality [Grade C (83,143)] and hypnosis [Grade C (144,145)] can be considered for treating pain associated with cancer surgery. Acupuncture [Grade C (146–148)] and electroacupuncture [Grade C (149,150)] can be considered for pain associated with aromatase inhibitor-associated musculoskeletal symptoms. For further details, see Supplementary Table 8, available online.

Taxane-Induced Neuropathy

Acetyl-L-carnitine is not recommended for prevention of taxane-induced neuropathy and was shown to increase neuropathy in one large study [Grade H (101)]. For further details, see Supplementary Table 9, available online.

Lymphedema

Manual lymph drainage [Grade C (151–157)] and low-frequency laser therapy and electrotherapy [Grade C (158,159)] can be considered for reducing arm volume and improving lymphedema-related quality of life, particularly among those breast cancer survivors who are unable to tolerate compression bandaging due to allergies or discomfort. For further details, see Supplementary Table 10, available online.

Vasomotor Symptoms

Acupuncture [Grade C (88,160–164)] and electroacupuncture [Grade C (165,166)] can be considered for reducing hot flashes in survivors. At the dose and formulations tested, soy isoflavone extracts or soy as food [Grade D (167–169)] cannot be recommended to prevent or treat hot flashes in breast cancer survivors because it has not been found to be efficacious. For further details, see Supplementary Table 11, available online.

Acute Skin Reaction From Radiation Therapy

Aloe vera gel [Grade D (170,171)] and hyaluronic acid [Grade D (172,173)] are not recommended to prevent or treat acute radiation skin reaction from radiation therapy due to lack of effect. For further details, see Supplementary Table 12, available online.

Other Outcomes

There are insufficient data from existing trials to make guideline-level recommendations on interventions to prevent and/or treat side effects and symptoms related to cognition, anemia, neutropenia/leukopenia, alopecia, cardiomyopathy and adherence to standard treatment. The search did not identify any eligible trials that addressed hepatic, renal, or gynecologic toxicities or side effects. For further details, see Supplementary Table 13, available online.

Suggestions for Future Research

To formulate trusted clinical guidelines, the Institute of Medicine recommends conducting a systematic review of the evidence and clearly and conservatively assessing the benefits and harms of all care options; a process followed for this review (21). Many trials available for review shared common limitations, including small study sizes, poorly reported or unstated delineation of outcomes (ie, primary, secondary, or exploratory outcomes), lack of standardized outcome measures, use of surrogate measures with limited clinical relevance, omission of toxicity and adverse event data, inadequate statistical methods, and lack of blinding and/or appropriate control groups. Future trials need to address and avoid these limitations. There are multiple challenges to identifying appropriate control groups and maintaining relevant blinding for natural products, acupuncture and mind–body therapies. However, these challenges are not insurmountable and many can be addressed in the study design phase. To improve the validity of future studies, it is critical that trials measure clinically relevant and standardized outcomes using validated tools and analyzed with accepted and appropriately chosen statistical methods to better allow for pooled analyses.

Similar to some trials of conventional supportive care interventions, many of the trials reviewed here did not assess drug interactions and/or long-term safety considerations. As a result, some of the natural products that had strong evidence on short-term effects, but lacked data on long-term safety and toxicity outcomes, were downgraded from a Grade B to a Grade C (eg, mistletoe). As potentially bioactive agents with the possibility of drug interactions, botanical products and dietary supplements should be studied with appropriate assays to detect drug interactions. If indicated, long-term clinical studies should be powered to identify positive and negative interaction effects on overall and disease-free/progression-free survival. Quality control standards on the formulation/composition and relevant bioactivity need to be expanded and uniformly adopted.

Key areas of unmet need were identified for future research. These include studies to address peripheral neuropathy, arthralgias, mucositis, fatigue, and cognitive dysfunction using large sample sizes with well-defined clinical characteristics. Although not sufficient for Grade A or B recommendations, there is promising evidence on the use of acupuncture for nausea, fatigue, anxiety, pain, and quality of life; the use of acupressure and ginseng for fatigue; the use of mistletoe for quality of life; the use of ginger for CINV, and the use of stress management techniques for improving mood, quality of life, and sleep. Low-cost strategies, such as the use of electronic medical records, and the utilization of established research networks, such as cooperative groups, can be efficient means to yield high quality and useful clinical outcomes data. Researchers can consider incorporating assessment of complementary and integrative therapy use and intervention effects to conventional treatment trials. Trials should investigate the comparative effectiveness of Grade A and B interventions to better inform patients and clinicians who are actively making decisions on the use of complementary and integrative interventions that have varying levels of benefit. Pragmatic and preference-based trials in real-world clinical and community settings will be important in establishing treatment effectiveness. These suggested strategies will require research funding prioritized to conduct preliminary

hypothesis testing trials to identify promising therapies, which can then be further tested in larger, more definitive trials using adequate statistical power, appropriately selected patients, longitudinal designs, validated endpoints, and optimized complementary and integrative medicine modalities.

Limitations

As with any systematic review, there are limitations to this process. This search targeted articles focused on the use of integrative therapies during active breast cancer treatment. We only reviewed primary analyses of randomized controlled trials and did not analyze other systematic reviews, meta-analyses, or observational studies. In addition, we only included trials that were comprised of a majority of breast cancer patients, which excluded a number of high-quality trials of similar interventions among other cancer patient populations. By using search criteria that started with articles published in 1990, we placed a higher value on more contemporary studies because these patient populations received treatments more comparable to current breast cancer treatment regimens, while recognizing that future guideline may include a separate set of criteria for meta-analyses and overviews. We took this conservative approach because no previous integrative oncology guidelines had been formulated using a highly systematic process.

A major challenge to interpreting this literature is the lack of standardization of interventions across trials using similar therapeutic approaches (eg, natural products and mind–body therapies). Such lack of standardization can make it complicated to apply and administer the guidelines, especially for natural products. In addition, some integrative therapies are applied in a variety of settings (early vs advanced stages disease, a spectrum of symptom severity), such that the clinical criteria for using some therapies may not be straightforward. However, many of the approaches identified here are low risk (eg, stress reduction), and the lack of standardized approaches may not greatly influence their clinical application. Future efforts focusing on increasing levels of reproducibility and standardization should be concentrated on interventions with higher risk profiles.

Though the search was detailed and clinically oriented, it may have missed some articles that addressed treatment-related effects following the treatment period. Similarly, there are a number of treatment-related side effects that are common across chemotherapy regimens and not limited to a specific cancer (eg, febrile neutropenia, blood counts, CINV). As this search was restricted to breast cancer patient populations, it may not have included the full range of legitimate trials that addressed the outcome of interest. All systematic reviews need to have a defined time period and be acknowledged as such. The field of integrative oncology is rapidly expanding and since the period of the search, a handful of trials were published on the use of yoga for mood and fatigue and quality of life, which may have upgraded the recommendations (174,175). Finally, a large number of breast cancer survivors use natural products following a diagnosis, and at this time, there is a paucity of data to inform clinical recommendations on such use.

Conclusions

Integrative therapies are commonly used by breast cancer survivors for many indications, including managing the side effects of cancer therapy and improving quality of life. Randomized controlled clinical trials in patients receiving treatment for breast cancer provide strong evidence (Grade A) on the use of behavioral therapies (eg, meditation/mindfulness, relaxation) and yoga for mood improvement in the context of depression and anxiety during cancer treatment. Lower grades of recommendations (Grade B) can be made for massage and stress management for mood improvement and energy conservation in the context of treatment-associated fatigue. A number of interventions for a diverse set of symptoms attained a Grade C, representing a significant dilemma for patients and health-care providers as they face decisions on whether or not to use or recommend these modalities. Grade C interventions are supported by some evidence from randomized controlled clinical trials, but do not have a large body of evidence to support their use. As such, Grade C interventions represent areas of greater need for additional research. Grade C interventions require shared decision making between patients and providers, a discussion of the risk-benefit for all available treatments, and monitoring for efficacy, futility, and harm and balanced against the availability of conventional treatments. Apart from using ginseng for fatigue, ginger for CINV and mistletoe to improve quality of life (all Grade C), recommendations cannot be made for other botanical products or dietary supplements, and harm has been attributed to acetyl-L-carnitine for the prevention of neuropathy. Some of the natural products had sufficient efficacy data but lacked long-term safety data to warrant a higher grade. Given the limited number of Grade A and Grade B recommendations, clinicians should engage patients in shared decision making using evidence-based projected benefits and harms that reflect patient values and preferences, as well as acknowledge their clinical prognosis. In the decision-making process, clinicians and patients can make use of high-quality resources to summarize potential side effects and interactions of natural products, such as Natural Standard (https://naturalmedicines.therapeuticresearch.com). The field of integrative oncology represents a high priority for research as the overarching goal is to identify safe and efficacious integrative and conventional therapies to address unmet patient needs.

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